

Review Article

The role of innate immunity in spontaneous regression of cancer

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Abstract

Nature has provided us with infections – acute and chronic – and these infections have both harmful and beneficial effects on the human system. Worldwide, a number of chronic infections are associated with a risk of cancer, but it is also known that cancer regresses when associated with acute infections such as bacterial, viral, fungal, protozoal, etc. Acute infections are known to cure chronic diseases since the time of Hippocrates. The benefits of these fever producing acute infections has been applied in cancer vaccinology such as the Coley's toxins. Immune cells like the natural killer cells, macrophages and dendritic cells have taken greater precedence in cancer immunity than ever before. This review provides an insight into the benefits of fever and its role in prevention of cancer, the significance of common infections in cancer regression, the dual nature of our immune system and the role of the often overlooked primary innate immunity in tumor immunology and spontaneous regression of cancer.

Key words: Acute infections, fever, innate immunity, leukocytes, tumor regression

Introduction

Spontaneous regression is the partial or complete disappearance of a malignant tumor proven by microscopic examination in the absence of any substantial treatment.^[1,2] It occurs in most types of cancer and was recorded in the medical literature as early as 1742.^[3] Cancer regression is not a novel phenomenon but has been observed for thousands of years. The earliest references of cancer immunotherapy and regression date back to the times of Egyptian chief physician Imhotep (2600 BC), who recommended poultice followed by incision of the tumor as a treatment which would result in its infection and therefore its regression.^[4]

The word spontaneous implies without any apparent

cause,^[4] and regression is defined as a decrease in the size of the tumor or in the extent of cancer in the body according to the National Cancer Institute (NCI).^[5] Spontaneous regressions are known to be commonly associated with acute infections, vaccine therapy and incomplete surgical removal of the tumor.^[4,6] Regression is more commonly associated with groups of tumors like the embryonal tumors in children, carcinoma of the female breast, chorionepithelioma, adenocarcinoma of the kidney, neuroblastoma, malignant melanoma, sarcomas, carcinoma of the bladder and skin.^[1,7]

Cancer, infectious agents and fever

A review of reports suggests that regression is often preceded by acute infections, which bring about a strong immunological response and therefore fever. A strong febrile reaction from a natural or induced acute infection was the most common symptom associated with tumor regression.^[8] Fever enhances host defense against infections as concluded by studies such as the clinical studies on rhinovirus infected adults which found increased viral shedding, nasal symptoms, and decreased antibody response when antipyretics were administered to combat the illness.^[9] It was found in another study

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in children with malaria that antipyretic drug therapy significantly impaired plasma clearance of the malarial parasite compared to untreated individuals.^[10] Data from studies also show that frequent administration of antipyretics to children with infectious disease may lead to a worsening of their illness, with progression of acute fever to pneumonia in children receiving higher doses of paracetamol during the initial stages of fever.^[11]

Antipyretic use was also associated with an increased duration and severity of illness in children affected with chicken pox.^[12] Previous reports suggest that occurrence of fever in childhood or adulthood may protect against a later onset of malignant disease and that spontaneous remissions are often preceded by feverish infections.^[13]

Prior fever was recorded in 25–80% of documented cases of spontaneous regression of cancer. Diamond and Luhbyq in 1951 reported 26 spontaneous remissions in a cohort of 300 cases of childhood leukemia; 80% was accompanied by infection.^[12] Stephenson and colleagues in 1971 investigated 224 cases of spontaneous regression and reported that in 62 cases (28%), regression was preceded by either an infection or a persistent temperature elevation. Rohdenburg in his observation stated that regression was often accompanied by high temperature of several days duration. The most frequent infection was erysipelas, an infection causing particularly high fever, producing exotoxins that can function as superantigens, which gives rise to polyclonal expansion of T cells. Regression was also associated with small pox, pneumonia, malaria and acute tuberculosis.^[6]

Unlike the acute febrile response of an acute infection, chronic infection generally represents a failed immune response to disease and is associated with tumor promotion. Yet, even chronic infections may have temporary periods of benefit as during an acute flare-up or concurrent illness.^[4]

Cancer is known to be associated with certain chronic infections. Infections are responsible for about 15% of malignancies worldwide. According to Noble Prize winning virologist Zur Hausen, 10–20% of cancers are caused by viruses worldwide.^[14] The estimated total of infection-attributable cancer in the year 2002 is 1.9 million cases or 17.8% of the global cancer burden. The principal agents are the bacterium *Helicobacter pylori* (5.5% of all cancers), the human papilloma viruses (5.2%), the hepatitis B and C viruses (4.9%), Epstein-Barr virus (1%), human immunodeficiency virus (HIV) together with the human herpes virus 8 (0.9%).^[15] Viruses like the EBV have been implicated in B-cell lymphomas, nasopharyngeal cancers and

Burkitts lymphoma. HPV is associated with nearly all cervical cancers, oral, head and neck cancers, and Kaposi's sarcoma. The hepatitis B and C viruses have been implicated in about 80% of hepatic cancers, HPV and bacteria like *H. pylori* are implicated in gastric carcinomas, to name a few.^[14,15]

But infectious agents, like many of nature's creations, can also play an alternative role. The earliest notion that a history of infectious disease can result in a reduced risk of cancer was reported in 1899 when the British cancer researcher D'arcy Power observed, "Where malaria is common, cancer is rare".^[16] At least 15 investigations between 1929 and 1991, including eight case-controlled studies, have examined the link between infectious disease and cancer and all but one have found that a history of infectious disease reduces the risk of cancer. In a 1991 study of 255 patients with cancers of the stomach, colon, rectum, breast and ovary, compared to 255 population controls and 230 hospital controls, a prior history of multiple common colds or stomach flu was found to be associated with a decreased risk of cancer.^[17]

The earliest study on the effects of acute infections on inoperable sarcomas was done by German physician W. Busch who reported that he had observed a patient's tumor "re-absorbed" after a high fever. Dr. Busch associated tumor regression with acute infections such as erysipelas as early as 1867.^[18] Some interesting facets of spontaneous regression include both the diversity of organisms, for example, with bacterial, fungal, viral, and protozoal pathogens, and also interestingly infections that elicit a humoral immune response, for example, *Aspergillus*, malaria, *Trichinella*, trypanosome, and also the speed at which these regressions occurred.^[19]

Cancer cells resemble normal host cells and have been successfully evading the host defense system and are also able to grow and promote themselves at the expense of the host. The cancer cells can evade the immune cells by lowering antigenicity with fewer major histocompatibility complex (MHC) class I molecules on their surface,^[20] improving immunotolerance and secreting cytokine transforming growth factor (TGF)- β which inhibits the activities of macrophages and lymphocytes.^[21] Regressions in some advanced malignancies provoke us to think otherwise and inspire us to find the link between an active cancer toxic immune system and immune evading cancer cells. Tumor cells evolve due to their inherent genetic instability, producing variants leading to successive cell populations with different immunogenicity, and thus constantly challenge the host defense cells. Thus impressing the need of a powerful stimulus (acute infection) that can enhance and

activate the immune system.^[22]

The inherent inefficiency of the immune system has given rise to numerous and highly expensive cytotoxic cancer therapies over the past few decades with no real benefits translated to the patient such as a cure or decreasing the chances of patient dying from cancer.^[23] As cancer is a growing menace, even so in developed nations, according to the World Health Organization (WHO), the global cancer rates could increase by 50% in the next 15 years. The cost of cancer therapy will be enormous and a huge burden on the national health policies as well as the patient.^[24]

History tells us that spontaneous regression has been associated with acute infections and Coley's toxin therapy, in which immunity has a large role to play. Though the spontaneous innate system has largely been ignored in cancer studies of the recent past, presently many authors attribute spontaneous regression to the older and immediate innate immunity. Research into these aspects has thrown a whole new perspective onto the role of innate immunity in cancer recovery.^[4]

Discussion

In a path-breaking profound observation, Cugnenc *et al*, observed in 2005 that the location and density of T cells within colorectal tumors is a better predictor of patient survival than tumor classification by size and spread.^[25] An interesting facet that is noticed in spontaneous regression is both the diversity of organisms associated and the speed at which the regression occurs. Therefore, it has been proposed that regression is mostly linked to the cell-mediated immunity rather than the humoral immunity.^[19]

The human immune system can be broadly divided into two parts, the innate and the adaptive. The evolutionarily older innate immune system reacts within minutes after the invading pathogens are encountered. The adaptive system, which employs evolutionarily younger and more customized tools, takes longer time from days to weeks to generate specialized antibodies and T cells to attack threats.^[22]

The innate immune system

The innate system consists of natural anatomical barriers, such as skin and mucous membranes, and physiological barriers like elevation of temperature and acid in the stomach to digest harmful bacteria as well as the cells of first defense. Innate immunity is effective against a variety of infectious agents that have common features recognized by phagocytic cells but has no immunological memory against previous exposure and

is antigen independent.^[26]

The innate system is composed mainly of natural killer (NK) cells, polymorphonucleocytes (PMN) and macrophages, and is most directly involved in tumor immunology. These cells also participate in the adaptive response and form an important and vital bridge between the two arms of the immune system.^[22] It recognizes non-self molecules according to a specific pattern. Another feature of the innate immune system is the complement, a group of inactive proteins in the blood which are activated in the presence of pathogens and non-self cells and cause cell lysis.^[27]

The ability to recognize a non-self cell such as a pathogen is fundamental to all innate cells. Pathogen recognition by the innate cells occurs by pathogen-associated molecular patterns (PAMPs) found in all microorganisms and pattern recognition receptors (PRRs) found in all the cells of the innate defense system. A PAMP is a molecular pattern that is unique to microorganisms. Every PAMP has a corresponding unique PRR in one or more of the innate cells, which helps in latching onto and identifying the invading pathogen.^[28] Examples of PAMPs are lipopolysaccharides (endotoxin), peptidoglycan (cell walls), lipoproteins (bacterial capsules), hypomethylated DNA (such as CpG found in bacteria and other parasites), double-stranded DNA as found in viruses, and a molecule called flagellin that is found in bacterial flagella.^[29]

The NK [Figure 1] cells are lymphogranular cells having an ability to kill the intruding pathogens and are the most important cells of the system. These killer cells are found in the innate and the adaptive system as well. They originate from the lymphoid progenitor and migrate to the secondary lymphoid tissues. On provocation, the NK cells burst forth from the tonsils, lymph nodes and spleen, and destroy

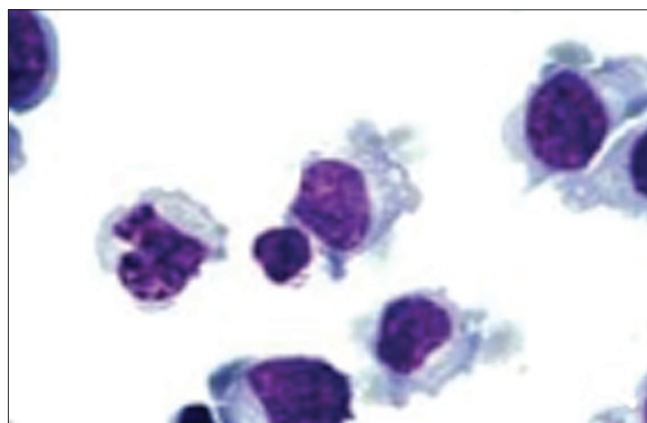


Figure 1: Natural killer cells, SUNY Upstate Medical University

infected and cancerous cells while the immune T cells and B cells are still mobilizing. They do not require memory from previous encounter and target virus infected cells and tumor cells and are the first line of defense. They also secrete lymphokines which signal and modulate emerging B and T cells.^[30] Recent research highlights the fact that NK cells are also regulatory cells engaged in reciprocal interactions with dendritic cells, macrophages, T cells and endothelial cells. NK cells can thus limit or exacerbate immune responses.^[31]

The role of adaptive immunity

The adaptive or acquired immunity is antigen specific, slower and possesses immune memory against future attacks. The adaptive response follows the innate response and is dependent on specific recognition of antigen by antigen receptors present on the cell surface. The two types of adaptive immunity are cell-mediated immunity and humoral immunity. T lymphocytes are responsible for cell-mediated immunity and B lymphocytes for humoral immunity. B cells play a role in destroying tumor cells by complement-mediated lysis and facilitating antibody-dependant cell-mediated cytotoxicity.^[31] The cytotoxic T cells (CTC) and the natural killer T (NKT) cells are two important T cells which are involved in lysis of tumor cells. The CTC kill target cells with MHC-antigen complex on the cell wall, while the NKT cells actively search and kill tumor cells and play a crucial role in preventing metastasis of cancer. Affected cells which do not display MHC-antigen complex are targeted by the NK cells.^[30,32]

Linking the innate and adaptive immune systems are dendritic cells that hugely play an important role in restraining cancer. Dendritic cells migrate and are found patrolling below and within the epidermis and mucous membranes in the mouth, nose, ear and colon. These cells produce antigens from ingested pathogens and cell debris, carry them to the lymph nodes and display them on their surfaces to T cells. Thus, the T cells and B cells are stimulated to customize their immune attacks.^[22]

To be functionally active, dendritic cells need certain danger signals to activate them, such as the PAMPs that are present on bacteria and viruses but are absent on the cancer cells. Acute infection in a cancer patient activates these cells into recognizing cancer cells and presents them to T cells whereby the patient benefits from an active and powered immune response that fights the infection as well as the cancer – clearly a situation of dual advantage.^[28]

Tumor immunology

The innate immune system constantly kills cancer cells inside our body. This is one of the reasons why not all

of us develop cancer. A huge variability in the ability to kill cancer cells was found between different individuals. Some people's white blood cells managed to kill more than 97% of the cancerous cells in less than 24 hours, while others only managed to kill about 2% in the same time. Activity of the immune cells varies from person to person and may be genetically inherited.^[33] In a study, NK cell activity was evaluated in children with acute lymphocytic and acute myelogenous leukemia and it was noted that there was an absolute decrease in the activity of the NK cells and also an absolute decrease in the lytic potential of these cells.^[34]

In Coley's experiments, it was noted that regression occurred within hours of injecting the toxins and that the tumor recurred from the residual tumor on discontinuing the treatment even for a single day, suggesting that the antitumor activity was mediated by the primary innate and nonspecific immune response rather than a slower specific adaptive immunity which takes days to a week to get activated. Coley had recommended daily or alternative day vaccine injections in treating his patients for its effectiveness,^[4] and it is likely that fever has an important role in this scenario. As Klemens Trieb and colleagues reported back in 1994, cancer cells can be more vulnerable to heat than normal cells. Fever produces heat and may produce an unusually high amount of cell debris from cancer cells, possibly resulting in more cancer cell antigens being collected by dendritic cells. High amounts of antigen can stimulate and activate the immune system more efficiently.^[35] Fever therapy by Coley's toxins or mixed bacterial vaccines provokes a powerful reaction of the immune system through induction of interferon, augmentation of NK cell activity, stimulation of lymphoid tissues, activation of macrophages, induction of serum factor that causes necrosis of tumors, as well as stimulation of interleukin 2.^[36]

Pyrogenic substances and hyperthermia have also been successfully administered in palliative and curative treatment protocols for metastatic cancer to mimic the physiological response to fever.^[37] In contrast to hyperthermia, fever is accompanied by diverse immunological changes, notably, an increase in biochemical reaction rates and enhanced leukocyte proliferation, maturation, and activation. Febrile thermogenesis (e.g., chills, shivering, etc) is associated with an increase in the metabolic rate by two to three times, while fever maintenance has been associated with a 30–50% increase in the metabolic rate.^[4]

Inherent duality of repair and defense

Our immune system basically acts from a defensive or a reparative mode of function; this is an inherent duality

of the system. Evidence supports that to activate the lytic potential of our immune system, the tumor has to be infected; otherwise, the tumor releases chemokines that generate a reparative response from the immune system akin to a sterile wound, which essentially supports wound healing or tumor progression by growth factor production, angiogenesis, etc. This is primarily due to the dual nature of our immune system of defense and repair.^[38,39]

Leukocytes, particularly macrophages, play an important role in tumor regression. They are found in large numbers in growing tumors and are capable of prolonged survival in acidic wound environment. Macrophages contribute to production, mobilization, activation and regulation of all immune cells. Macrophages are also involved in phagocytosis and intracellular killing of microorganisms and extracellular killing of altered self-target cells. They are pluripotent cells, secrete a wide range of growth factors and contribute to tissue repair. A shift to the defensive mode reduces the production of these growth factors that promote tumor growth.^[40]

A delicate balance exists between immune-mediated tumor growth and tumor regression by the macrophages. Thus, the presence of hypoxia or necrosis in an otherwise sterile tumor can induce the release of factors that stimulate tumor growth, while the introduction of Coley's vaccine or other bacterial, viral, or fungal antigens can shift the balance back toward a defensive immune response. A final key factor contributing to tumor regression involves the direct killing of tumor cells by macrophages.^[41]

So, why have not immune products like interleukins, interferons, and monoclonal antibodies, etc., which are used in cancer therapy gained substantial appreciation in the treatment of cancer? Because synthesis of these products requires immense expertise and facilities, it is easier to prepare vaccines that simulate an infection that triggers an acute immune response *in vivo*. Immune products are highly expensive and are mostly used as adjuncts and their effects at times are unpredictable which is largely because no single factor is responsible for cancer regression; rather, it is a cascade of complex immune reactions that are responsible for this effect.^[19] Moreover immunology is an emerging science and single cytokine therapies may result in much unique toxicity due to the fact that such treatments present an unnatural challenge. Some of the known toxicities of cytokine therapy include acute and chronic CNS toxicity, neuropsychiatric toxicity and fatal systemic inflammation.^[42,43]

Infections, either induced or natural, stimulate a multitude of cascading, interlinking and complex pathways of the immune system, simultaneously releasing numerous products in the right quantity and quality to combat the disease which may not be humanly possible to reproduce *in vitro*.^[19] Everson and Cole in 1968, in their summary of collected cases, acknowledged that some of the factors or mechanisms responsible for spontaneous regression are obscure or unknown in the light of present knowledge.

In conclusion, the role of the primary and innate immunity by induced or naturally occurring acute infections and the subsequent activation of the slower specific adaptive immunity play a vital role in fighting cancer. Infectious agents like the immune system are dual in nature and have both beneficial and harmful effects. Occurrence of fever and common cold significantly activates and prepares the immune system against virulent attacks in the future and the indiscriminate use of fever controlling drugs and antibiotics in common ailments should be curbed.^[4] Current research in the UK into the use of adenovirus or common cold virus to regress cancer is a step in harnessing body's own immunity to fight cancer.^[44] Feverish infection reduce would be malignant cells and its implications are profound.^[22]

It is important to remember the larger significance and beneficial aspects of the common flu and other fever causing self-limiting infections on the human population, especially during childhood, as it has a protective role in preventing dangerous and untreatable diseases like malignancy later in life.^[45]

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