THE ASSOCIATION BETWEEN THE IMMUNE SYSTEM AND MALIGNANCY: A BRIEF REVIEW

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Abstract
The immune system has evolved to protect the host from a universe of pathogenic microbes and eliminate toxic substances from the body. It is an interactive network of lymphoid organs, cells, humoral factors, and cytokines. The essential function of the immune system in host defence is best illustrated when it goes wrong: decreased activity results in severe infections and tumours of immunodeficiency, and increased activity in allergic and autoimmune disease. Immune cells scan for the occurrence of any molecule that they consider to be foreign to the body, and transformed cells acquire antigenicity, which is recognised as non-self. A specific immune response is generated, and it results in the proliferation of antigen-specific lymphocytes. Immunity is acquired when antibodies and T-cell receptors are expressed and up-regulated through the formation and release of lymphokines, chemokines and cytokines. Both innate and acquired immune systems interact to initiate antigenic responses against carcinomas. There is an increasing body of recent evidence to support the role that the immune system plays in eliminating pre-clinical cancers. Tumour infiltration by immune cells has been shown to have powerful prognostic significance in a host of cancer types. Cytotoxic therapies, including Low Level Laser Therapy (LILI) and chemotherapy, induce potentially immunogenic cell death, releasing tumour-associated antigens in the context of a ‘danger’ signal to the immune system. An understanding of the interaction between immune cells, tumour cells and treatment modalities will therefore guide the future combination of immunotherapy with conventional therapy to achieve optimal anti-tumour effects.

Keywords
Cancer, immune system, inflammation, therapy

INTRODUCTION
Humans are exposed to foreign organisms through swallowing, penetration of the skin and inhalation. Depending on both the virulence factors at its disposal and the integrity of host defence system mechanisms, these organisms would cause disease[1]. The association of immune cells and cancer was established by Balkwill and Mantovani[2]. The immune system is known to dominate spontaneous tumour development and infection inflammation, which is common with individuals with chronic inflammation and certain gene mutations that encode immune modifiers – namely, cytokines, proteases and signal transduction proteins[3, 4]. Neoplastic microenvironments also favour polarised chronic pro-tumorigenic inflammatory states. Such individuals have impaired T-lymphocytes and activation of their immune cells upsets a crucial balance and promotes cancer development[1-4].

Cancer arises as a result of a multi-step process leading from the initial benign transformation of cells through to invasive, metastatic disease[5]. It is a deadly (insidious) disease that progresses slowly, originating from mutant DNA sequences that change the direction of crucial pathways regulating homeostasis, cell survival and cell death. They are composed of multiple cell types, such as fibroblasts and epithelial cells, innate and adaptive immune cells, and cells that form blood and lymphatic vasculature, as well as specialised mesenchymal cell types that are unique to each tissue environment[6]. Fifteen percent of all human cancers are believed to be caused by infectious conditions[6]. Greater risk of cancer amongst individuals with frequent antibiotic regimens could be either because they are maintaining low-level chronic inflammation due to their natural immune defence mechanisms or because they fail to normalise their immune status following infection[6]. Aging and individual differences also play a role in cancer development among the general population[7]. The relationship between chronic immune activation and malignancy is associated with the development of tumours such as the lymphomas seen in Human Immunodeficiency Virus (HIV) induced Acquired Immunodeficiency Syndrome (AIDS), or Chronic Graft-versus-host disease (GVHD)[8]. This brief review will explore the interaction of the immune system and malignancy.

THE IMMUNE SYSTEM
The immune system is an interaction of lymphoid organs, humoral cell factors and cytokines to form a network, which becomes activated when something is wrong with the host defence[8]. The immune system can be classified into two arms, namely cell-mediated immunity and antibody-mediated immunity depending on the speed and specificity of the reaction of the immune response[5, 6]. It comprises several cell types and mediators that interact with non-immune cells and each other. These interactions form complex and dynamic networks to ensure protection against foreign pathogens; at the same time they tolerate auto antigens[6].

Cell populations (macrophages, dendritic cells (DCs), natural killers (NK) cells, and neutrophils) play a major role in both innate and acquired immunity[10] (Figure 1).
Principally, cytotoxic T lymphocytes (CTL) and NK cells are effector cells which produce cellular immune response to cancer[11]. DCs are the key components to CTL, i.e., (CD8+ T-cells) responses to tumours. They constitute a family of antigen-presenting cells (APC) defined by their morphology and their capacity to initiate primary immune responses[12]. The helper T (Th)-cells, or CD4+ T-cells, are the major regulator of virtually all immune system activities. These form a series of protein mediators called lymphokines, which act on other cells of the immune system and on bone marrow[11]. The immunological dysfunction associated with human cancer comprises changes within the immune network, including cytokine imbalance of Th1/Th2 origin. Without an immune response the antigen-specific T-cells may enter a state of tolerance or apoptosis[13]. The components of the immune system do not recognize or respond to defective genes, but recognise and respond to the abnormal proteins that the cancer-causing genes encode. The individual components of the immune system play a major role in cancer[11].

Innate Responses

Innate immunity is a mechanism whereby cells defend the host from infection by other organisms in a non-specific way. It involves a large number of different cell populations, namely epithelial cells, monocytes, macrophages, DCs, polymorphonuclear leucocytes (PMN), NK cells, and various lymphocyte subpopulations (e.g. CD5-positive B-lymphocytes and gamma / delta (gd T-lymphocytes), which bridge the division between innate and acquired immunity[14]. Two further families of molecules play major roles in acquired immunity: major histocompatibility complex (MHC) gene products and cytokines. They provide an essential link for cell-to-cell communication and components of the acquired (as well as the innate) immune response[15].

Cytokine formation, release, and target interactions form an important arm of the cellular response in growth, repair, and cell proliferation. Cytokines can amplify the on-going immune response by up-regulating the expression of HLA (human leukocyte antigen) and co-stimulatory molecules such as B7 on parenchyma cells and APC[11]. They also function in the activation of macrophages, other inflammatory cells and the production of antibodies by stimulated T-cells. A product of the complement cascade strongly activates phagocytosis by neutrophils and macrophages, which engulf non-self-proteins. This type of cellular event is called antibody-dependent cell-mediated cytotoxicity (ADCC), and has the advantage of enhancing T-cell activity[16]. The specificity of immune response resides in selective clonal proliferation of lymphocytes. NK cells form a line of defence against host cells that are stressed or cancerous. They express surface receptors that receive signals from the environment and determine their response to foreign or malignant cells by producing effector molecules. They can both directly suppress tumour growth and convey important information to the rest of the immune system[17]. When tissue homeostasis is disturbed, macrophages and mast cells immediately release soluble mediators, such as cytokines, chemokines, matrix remodelling proteases, reactive oxygen species (ROS), and bioactive mediators such as histamine. The macrophages and mast cells also induce mobilisation and infiltration of additional leucocytes into damaged tissue (inflammation), and activate vascular and fibroblast responses. This leads to elimination of invading organisms and initiation of local tissue repair, which resolves once the ‘wound’, is healed[18].

DCs take up foreign antigens, and migrate to lymphoid organs, where they present their antigens to adaptive immune cells. They play a key role between innate and adaptive immunity and rapidly respond to tissue injury without previous memory or antigenic specificity[18]. DCs can then present the tumour antigens on their surface, lodged within MHC molecules and activate T-cells. Once the T-cells are activated, they are capable of recognising and destroying antigen-expressing tumour cells. Antigen uptake receptors on dendritic cells provide efficient limitation of antigen specific adaptive immunity[18]. Innate immune responses are induced by pattern-associated pathogens

Figure 1: The relationship between innate and acquired immune systems. DCs are important in both innate and acquired immunity responding to tissue injury. DCs activate T-cells, recognize and destroy antigen-expressing tumour cells. Innate responses are induced by pathogens, recognized by toll-like receptors on macrophages. Cytokines participate in cancer development, cell proliferation and survival is regulated by TNF-α. Response to T and B-lymphocytes comes as a result of exposure. Th cells regulate the immune activities. Adapted from Kaisho, 2010.
(e.g., lipopolysaccharide (LPS), double-stranded (ds) RNA, CpG DNA). These pathogens are recognised by toll-like receptors on macrophages\(^{20}\) and by the natural killer cell surface receptors, NKG2D and other NKp receptor ligands expressed on infected cells\(^{20}\).

**Cancer development and innate immune responses**

Innate immune cells have huge capacity to produce cytokines, chemokines, metalloproteinases, ROS, histamine and other bioactive mediators for cell survival which enables them to participate in cancer development\(^{22, 23}\). Chemokines and their receptors are responsible for infiltration of lymphocytes into the tumour tissue\(^{21}\). Due to the ability for matrix metalloproteinases (MMPs) to regulate epithelial cell proliferation, angiogenesis, cancer development, tissue homeostasis and disease, it has been identified as a crucial immune cell-derived mediator\(^{24, 25}\). During acute inflammation, tumour necrosis factor-alpha (TNF-\(\alpha\)) another inflammatory cytokine is mobilised (Figure 2).

**Adaptive Responses**

Adaptive immunity is the ability for lymphocytes to undergo massive expansion from time to time. These begin with selected binding of T and B-lymphocyte and expansion of these selected cells to fight an antigen or pathogen\(^{30}\). Primary adaptive immune responses require direct interactions with mature APCs and a pro-inflammatory surrounding for antigen specific reactions of T-lymphocytes and B-lymphocytes. These reactions result in larger responses upon subsequent exposure to the same antigen\(^{30}\). When these pathways are activated, they efficiently remove invading pathogens, damaged cells and extracellular matrix (ECM) normalising cell proliferation and cell death pathways. This will enable re-epithelialisation and new ECM synthesis\(^{30}\).

**Adaptive immunity and cancer**

The role of adaptive immune cells in cancer development is still debatable. The relative risk (RR) of cancer varies depending on the organ site and cancer origin. In cases of infection by onco- genetic viruses, such as hepatitis virus and human T-lymphotropic virus type 1 (HTLV-1), viral antigen presentation by HLA class I and II molecules to T-cells, and subsequent T-cell mediated cytotoxicity and cytokine production, are also key elements in the control of infection\(^{3}\). The adaptive immune system can also differentially regulate cancer development within the same epithelial microenvironment, as a function of varied initiation. Natural killer T (NKT) cells have also been reported in cancer development. NK cell recognition is mediated by the opposing modulate cellular adhesion, and induce pro-inflammatory mediators, in addition to further recruitment of other innate and adaptive cell types\(^{20, 29}\). Suppression of anti-tumour adaptive immune responses by chronically activated innate immune cells can indirectly contribute to cancer development by allowing tumours to escape from immune surveillance\(^{30}\).

![Figure 2](image-url)

*Figure 2: Cancer could develop from chronic inflammatory conditions in a series of processes: Pro-inflammatory cytokines and angiogenic factors enhance COX-2 and cyclo-oxygenase induction. NF-\(\kappa\)B also increases proliferation and survival. Malignancy results from pre-carcinogenic exposures leading to alteration of the micro-environment of the affected tissue. cAMP (cyclic Adenosine monophosphate); PI3K (phosphatidylinositol-3-kinase); IL-1\(\beta\) (interleukin-1\(\beta\)); TNF-\(\alpha\) (tumour necrosis factor-\(\alpha\)); NF-\(\kappa\)B (nuclear factor-\(\kappa\)B); COX-2 (cyclo-oxygenase-2); TGF-\(\beta\) (transforming growth factor-\(\beta\)); VEGF (vascular endothelial growth factor); IGF-I (insulin-like growth factor-I); MIP (macrophage inhibitory factor); PGE2 (prostaglandin-E2). (Adapted from Bryne and Dalgleish, 2001)*\(^{30}\).
effects of two different types of NK receptors: activation and inhibitory receptors. The activation receptors recognise stress-induced ligands that are expressed on the target cell, and then transmit intracellular signals that initiate cytotoxicity\(^{[31]}\). The inhibitory receptors recognise cell-surface MHC class I molecules and generate counter-activating signals that block the induction of cytotoxicity. NK cells can also influence subsequent adaptive immune responses by releasing cytokines and chemokines that induce growth and differentiation of various immune cells\(^{[13]}\). They express certain NK cell markers and recognize glycolipid ligands presented by the MHC class I like molecule, cluster of differentiation 1 (CD1d)\(^{[32, 33]}\).

Ironically, the influence of NKT cells during cancer development is probably a consequence of their inherent capacity to produce both pro-inflammatory Th1 cytokines and anti-inflammatory Th2 cytokines; therefore, the nature and balance of surrounding stimuli might determine which type of NKT cell induced T-helper response dominates and contributes to malignant outcomes. CD4+ and CD8+ T-cells are important modulators of such tissue-damaging B-lymphocyte responses\(^{[34, 35]}\). Adaptive immunity has a crucial role in regulating and activating innate immune cells in affected tissues such as immunoglobulin deposition which contributes to chronic inflammation and disease pathogenesis\(^{[36]}\).

**CHRONIC INFLAMMATION, INFECTION AND CANCER**

Inflammation is a process of responding to trauma usually caused by microbial infection. This process occurs in a sequence whereby various soluble factors and infiltrating cells, such as lymphocytes and leukocytes, are involved interacting with each other in different stages. This involves recognition of tissue penetration by pathogens or tissue injury, infiltration of lymphocytes, eradication of pathogens and killing of infected cells, liquefaction of surrounding tissue to prevent microbial metastasis and finally healing of damaged tissue\(^{[37]}\).

Persistently activated immune cells usually characterise chronic infection through tissue destruction and repair, due to either irremovable injurious stimuli or a dysfunction in any component of the normal inflammatory response with sources of chronic inflammation. This includes infectious agents: basically physical and chemical agents such as environmental exposures and dietary carcinogens, sustained wounds and gastric fluids\(^{[38]}\). Chronic inflammation, arising as a result of chronic exposure to a non-infective irritant may also be associated with the development of malignant disease\(^{[39]}\). This occurs when tissue homeostasis is seriously disturbed by failing to engage or disengage an arm of the immune system which allows the entry of immune cells. Chronically activated myeloid suppressor cells and regulatory T-cells found in the circulation accumulate, initiating destruction within the tissues. Such destruction can result in excessive tissue remodelling, loss of tissue architecture protein and DNA alterations which may be due to oxidative stress, and, under certain circumstances, alters interactions between innate and adaptive immune cells. This alteration expresses oncogenes leading to increased risk of cancer development\(^{[40, 41]}\). How long and strongly inflammation will continue after pathogen infection will depend mainly on the immunological features of the initial response. Cell proliferation does not by itself induce cancer but certain growth and survival factors enriched at sites of inflammation do.

Once tissue trauma has healed, the inflammation associated with cell proliferation required for tissue-regeneration ends. The cytokine cascade plays an important role in speeding as well as suppression of the immune response to pathogens. When initiated at sites of persistent inflammation continue to proliferate, they interact with inflammatory cells and growth factors such as TNF-α, a crucial step in carcinogenesis. In fact, many cancers are thought to be associated with inflammation caused by immunologically uncontrolled infections\(^{[42]}\). Among many cancers in which inflammation is considered to be involved, some may also be associated with production of carcinogenic proteins by infected microbes. Some examples are oncoproteins CagA by *Helicobacter pylori* in gastric cancer and oncoproteins X by hepatitis B virus (HBV)\(^{[43]}\).

** IMMUNE DIRECTED APOPTOSIS OF CANCER**

T-lymphocytes play a major role in the destruction of tumour cells. The immune system identifies tumour cells as “non-self” by several mechanisms (Figure 3), including recruitment of programmed cell death receptors that cause apoptosis of these cells\(^{[50]}\). However, tumour cells neutralise the immune system by evading detection and thereby prevent an immune response. The sensitised T-cells can affect killing of tumour cells by means of the lymphokines that they release. When these lymphokines are released, they mobilise and activate B-cells through B-cell growth factors and B-cell differentiation factors\(^{[51]}\). Macrophages and NK cells also exert tumour-killing effects through other mechanisms\(^{[52]}\).

On the other hand cancer cells may stimulate the immune system to express blocking antibodies, which cannot activate complement. This also means that no C3a or C3b is formed. Complement forms part of the innate immune system, it is sometimes recruited and brought to work by the adaptive immune system. As the disease progresses, there is associated decrease in immunity which results in a progressive fall in response to all foreign antigens\(^{[53]}\). Tumour cell death induced by conventional treatments releases a host of tumour associated antigens (TAAs)
which induces tumour cell death in order to stimulate an antitu-
mour immune response. Both radiotherapy and chemotherapy
have been assumed to antagonise any priming of the immune
system, by inhibiting lymphocyte division and inducing lym-
phocyte death\[54\]. Tumour cell apoptosis induced by these treat-
ments is considered non-immunogenic\[55\].

ROLE OF LILI IN THE ACTIVATION OF THE IMMUNE SYS-
TEM TOWARDS INHIBITION OR REDUCTION OF CANCER
DEVELOPMENT

LILI is a non-invasive form of treatment using low energy la-
sers. When these lasers are applied to tissue, they stimulate
biological responses, photochemical and physical responses in
photoreceptor molecules within the cell\[56\]. It has been shown
to regulate the body’s immune response locally and consist-
etly. It impacts cytokine production and heat shock protein
synthesis\[57\]. This response includes ATP production, control of
ROS\[58-60\] and induction of transcription factors such as activa-
tion protein-1 (AP-1), NF-κβ, etc.\[61-63\]. This redox process occurs
through the release of ROS\[64\]. A series of cellular processes
result from this response namely cell proliferation and migra-
tion, change of cytokine levels, growth factors, inflammatory
mediators and gene up-regulation. It also leads to oxygenation
in the tissues.

These factors may either increase or decrease depending on the
wavelength, dose and intensity of the light\[65, 66\]. This process
has been known over the years to reduce pain, inflammation,
promote wound healing, prevent cell damage, etc\[67\]. Immun-
otherapy could be another useful method of cancer treatment.
It does not only destroy the initial tumour but sensitises the
immune system to destroy every remaining tumour\[68\]. DCs, ac-
cumulated as a response to an inflammatory response, phago-
cytise the primary tumour cells, mature and present to the T-
lymphocytes. These lymphocytes become activated and attract
the chemokines which then move to the site of the remaining
tumour and destroy it.

CONCLUSION

Cancer and its environment represent a system of complex
interacting factors which includes the immune response and
cellular control pathways. Genes which have been rearranged
send signals to T and B-lymphocytes express surface recep-
tors. The B-cells recognise a single antigenic site on a protein
against which an antibody reacts on intact proteins. The T-cells
recognise antigens degraded into peptides and form complexes
with MHC molecules on the cell surface. Antigen specific rec-
ognition plus signals from co-stimulatory molecules causes an
intracellular signalling cascade that influences transcription
factors in the cell nucleus. These transcription factors influence
the expression of various genes, cytokines and effectors leading
to an immune response. The changes lead to the production of
tumour antigens that are presented on MHC molecules and
are recognised by the immune system as non-self. Some may
be eradicated by the immune system by immune surveillance
before they are clinically evident or through the combination of
immune and conventional therapy.

Malignant transformation is accompanied by mutations or al-
tered expression of oncogenes within the malignant cells. It is
possible to say that imbalanced or altered adaptive-immune-
cell interactions represent underlying mechanisms that regulate
the onset and/or maintenance of chronic inflammation that is
associated with cancer development since Immunoglobulin G
deposition is found in human pre-malignant and malignant tis-
sues. The occurrence of cancers, despite a functioning immune
system, and the probable antigenic similarity of cancers to the
normal tissue in which they originate, has led to doubt that the

\[Figure 3: Innate and acquired immunity interplay against tumour cells. Natural Killer cells in the innate
immune response CD 36, MHC class I chain-related (MIC) A/B respectively are receptors that can directly
activate or inhibit innate immunity. Acquired immunity is activated after phagocytosis of tumour cells by an
APC. MHC 1 and 11 antigenic molecules are made available to either CD8 or CD4 T cells. Once activated,
there is cytotoxicity and secretion of cytokines to initiate the immune response towards the tumour cells\[53\].\]
immune system has a significant role in cancer development and progression\[^{[4]}\].

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