Role of Innate Immune System in Cancer Development: Pro-Or-Anti Tumorigenesis?

Mohamed M. El-Khawanky
Assistant Professor of Clinical Hematopathology
College of Medicine, Najran University, Saudi Arabia
mmalkhaoanki@nu.edu.sa

Type of Publication: Review Paper
Conflicts of Interest: Nil

ABSTRACT
The innate immune system has a crucial role in the early defense against cancer through the activation of innate immune pattern recognition receptors, as several cancers are immunogenic however cancer cells develop various mechanisms to escape immune system attacks. It is axiomatic to say that the innate immune cells defense against the development of cancer cells, but some innate immune cells are implicated in promoting the growth and spread of cancer cells. Understanding the role of the innate immune cells in eliminating cancer cells increases the effectiveness of immunotherapy through their activation or inhibition. In this study, we shed light on the role of the innate immune cells in terms of pro-tumor and anti-tumor activities. Through understanding their mechanisms, we can employ the innate cells better for cancer cell elimination.

Keywords: Innate, Immune system, Cancer, Immunosurveillance, Immunoediting.

INTRODUCTION
Understanding the role of the immune system in chasing cancer cells increases the possibility of immunotherapy for cancer elimination. Because of the immunogenicity of some cancers resulting from the high mutational rate, the innate and adaptive immune systems have established roles in immune protection against oncogenesis through various mechanisms [1].

The innate immune system provides an early defense against cancer cells through non-specific patterns identification and adaptive immune system induction [2]. Contrary, the hallmark of the adaptive immunity being an antigen specific recognition and the generation of specific long-term memory against cancer cells [3]. Basically, the adaptive immune system comprises two classes of cells, T- and B-cells.

Several studies have showed the importance of the immune system in controlling cancer and have reported that immune cells such as natural killer (NK) cells, dendritic cells (DCs), CD8+ T lymphocytes can limit the outgrowth of tumor cells [3-4].

Although we often see the immune system acts as a tumor suppressor, other times it is a tumor growth stimulant. These antagonistic effects have complex implications for tumor progression, cancer elimination, and hence affect the immunotherapy development [5].

Cancer cells express two types of antigens that stimulate the immune system: one is a tumor-specific antigen unique to cancer cells, and another is a tumor-associated antigen that is expressed by cancer and normal cells [6].

The endogenous alteration of the immunogenic configuration of cancer to escape the immune system defense is known as the “cancer immunoediting hypothesis” [7].

The process of immunoediting starts with the immune recognition of cancer cells for elimination, then equilibrium that keeps the tumor cells in a
quiescent state and ends with immune evasion, and grows into an immune-resistant type [8]. The surviving immune-resistant cancer cells adopt various mechanisms to inhibit or overcome the cytotoxic response of CD8 T-cells, tumor-associated macrophages and NK cells [9].

This study briefly describes the role of innate immune cells in cancer development, whether it is anti-or pro-carcinogenic (figure 1).

![Diagram](http://www.biorender.com)

**Figure 1**: Response of innate immune cells to variant cytokines and growth factors.

GM-CSF: granulocyte-macrophage colony-stimulating factor, ILCs: innate lymphoid cells, TAM: tumor-associated macrophages, MDSC: myeloid-derived suppressor cells, NO: nitric oxide, TGF-β: transforming growth factor beta, NK: natural killer cell. Figure was prepared using BioRender (http://www.biorender.com)

**ROLE OF INNATE IMMUNE CELLS IN CANCER**

The results of antibody depletion and knockout mice studies show an important role for innate immunity in immune surveillance in genetic models of malignancy. Several studies have shown that tumors emerging in wild-type mice differ phenotypically and genetically from tumors that occur in mice lacking innate immune cells, suggesting that innate immunity has a crucial role in defense against cancer [10].

**1- Tumor-associated macrophages (TAM)**

Tumor-associated macrophages (TAMs) have a crucial role in the development, survival, and growth of cancer cells. TAM can be divided into two types (M1 and M2), which play different roles. M1-polarized macrophages secrete cytokines that boost the inflammatory process. However, M2 macrophages exhibit anti-inflammatory effects.
Regarding to the oxygen availability to tumor cells and tumor stage, TAMs are differentiated either to M1 or M2 macrophages [11].

In the early stages of tumor development at the normoxic tissues, type 1 macrophage (M1) permeates the tumor microenvironment releasing pro-inflammatory cytokines and chemokines to engage and boost Th1 and NK cell proliferation and differentiation in the immune surveillance context against cancer cells. [12].

In contrast, in late stages of and hypoxic tumor tissues, TAMs differentiate into type 2 macrophages (M2), releasing CCL17 and CCL24 factors that promote Th2 proliferation and differentiation and recruit regulatory T cells (T-regs) in favor of tumor growth. In addition, M2 macrophages support tissue repair and promote angiogenesis through the production of VEGF and translation of growth factor β1 (TGF-β), facilitating the metastasis of cancer cells [13].

2- Dendritic Cells

Dendritic Cells (DC) “tree-like cells” are responsible for the initiation of adaptive immune responses through antigen process and presentation to T-cells, establishing a primary link between the innate immune cells and adaptive immunity [14].

By immunophenotypic and genetic profiling, dendritic cells are classified into lymphoid and myeloid DCs with distinct subgroups. [15].

Protection against cancer cell growth and progression is one of the most influential features. Pulsing of DCs with killed ovarian tumor cells has been found to activate tumor-specific blood-derived T cells secreting IFN-γ upon experiencing autologous tumor cells [16]. Otherwise, upon the committed myeloid DCs are transferred to the cancer patient, the tumor produces and recruits mediators that suppress the proliferation and function of DCs, compromising the antitumor immunity [17].

3- Myeloid-derived suppressor cells

Myeloid-derived suppressive cells (MDSCs) are a heterogeneous group of immature myeloid cells that not developed into macrophages, dendritic cells or granulocytes. They are scanty in the peripheral circulation and are capable of suppressing the immune response. MDSCs are seen in a higher density during cancer, infection, and inflammatory diseases [13, 18].

Human MDSCs have been identified as CD14+, CD11b+, CD33+, without the co-expression of the MHC Class-II molecule HLA-DR [29]. In mice, MDSCs are subdivided into two separate subsets according to the expression of Ly-6C and Ly-6 G: monocytic-MDSCs (M-MDSCs, CD11b+Ly6G-Ly6Chigh) and polymorphonuclear or granulocytic-MDSCs (PMN / GMDSCs, CD11b+Ly6G+Ly6Clow) [19].

Via nitric oxide, reactive oxygen species, and TGF-β secretion, these MDSCs induce suppressive immune responses and regulate T cell functions while promoting T-reg function and boosting anti-inflammatory responses [20].

After migration of MDSCs to the tumor microenvironment they would normally differentiate, it is postulated that cytokines and cellular factors in the tumor microenvironment are believed to prevent MDSCs differentiation and maturation instead of promoting expansion and activation of the immature myeloid cell population [13], whether recent studies have indicated that MDSCs only block the immune surveillance that boosts the process of tumorigenesis [21].

It was reported that circulating MDSCs have increased in early and late cancer patient stages significantly, as well as with the metastatic cancer and correlated with poor clinical outcome. Besides, MDSCs accelerate angiogenesis, tumor progression, and metastasis. There is ample evidence showing that tumors with increased MDSC infiltration are associated with poor patient prognosis and poor cancer immunotherapy response [22].

While the certain function of the MDSC is still enigma, several studies tried to block their activities to increase the immunity surveillance against the cancer cells. Treatments targeting M-MDSCs in multiple myeloma studies enhanced therapeutic outcomes for MM patients. Transfusing MDSCs, on the other hand, will be a potentially beneficial treatment to minimize GVHD post-allo-HSCT for various hematological malignancies and disorders [23].

4) Mast cells
Mast cells originate from CD34+ pluripotent hematopoietic stem cells and eventually, after passing through blood circulation, complete their maturation in tissues [24].

Several biologically active factors involved in tumor growth modulation can be secreted by mast cells [25]. They comprise both pro-tumor and anti-tumor factors, depending on a variety of factors, including the presence of MCs within or at the margin of the microenvironment of the tumor [24].

MCs are capable of facilitating the tumor vascularization and promoting tumor invasiveness through the release of IL-8, VEGF, FGF-2, NGF, heparin, tryptase, chymase, TGF-β, MMP-2 and MMP-9 that correlated with poor prognosis, increased metastasis and reduced survival in several types of human cancer [27], such as different types of Hodgkin’s and non-Hodgkin’s lymphoma [28], and plasmacytoma [29].

Via the release of IL-8, VEGF, FGF-2, NGF, heparin, tryptase, chymase, TGF-β, MMP-2 and MMP-9 by mast cells, they are capable of boosting tumor vascularization and promoting tumor invasiveness. Mast cells and the increased levels of secreted cytokines are correlated with poor prognosis, increased metastasis, and decreased survival in several types of human cancer [27], such as various types of Hodgkin’s lymphoma and non-Hodgkin’s lymphoma [28].

Contrary, other cytokines released by MCs including IL-1, IL-4, IL-8, IL-6, MCP-3, MCP-4, TNF-α, IFN-γ, LTB4, and chymase promote the emerging of inflammatory process inside the tumor mass, inhibiting tumor cell growth, and inducing tumor cell apoptosis, as reported in a breast cancer study [30].

Upon activation of MCs, the released mediators recruit neutrophils, macrophages, and eosinophils predominantly from the innate immune system and encourage the acquired immune system cells (B and T cells) to develop an antitumor immune response [31]. In mice expressing adenocarcinoma of prostate, the pharmacological targeting of mast cell function by sodium cromoglycate increased the aggressiveness of tumor behaviour, suggesting that environmental mast cells can exert anti-tumor effects depending on the cancer cell type [32].

5) Neutrophils

Neutrophils are derived from the precursor of myeloid hematopoietic cells; they constitute the main cellular components of white blood cells and the innate immune system [33].

The neutrophil population displays a heterogeneous phenotype and versatility of action. However, the polarization states of the tumor-associated neutrophils (TANs) are still indefinite in terms of anti- and pro-tumor properties [34].

Neutrophils infiltrating the tumors, known as tumor-associated neutrophils (TANs), have a significant role in oncogenesis. Indeed, multiple studies have shown that neutrophils are involved in cancer development, tumor progression, and associated with worse prognosis for cancer patients. However, some clinical evidence suggested that neutrophils may have an effective antitumor effect [35].

Neutrophils are therefore categorized into two groups, N1 (anti-tumor neutrophil) and N2 (pro-tumor neutrophil), preferring one of the antagonistic interactions between CXCR2 and CXCR4 that maintains neutrophil homeostasis [36].

CXCR2 upregulation increases the mobilization of mature neutrophils to the peripheral circulation and enhances the process of oncogenesis, while CXCR4 upregulation contributes to the backing of neutrophils to the bone marrow and is phagocytosed by macrophages that enhance the anti-tumor property [37].

Experimentally, neutrophils have been involved in nearly every stage of the oncogenic process from tumor cell proliferation, angiogenesis, metastasis, and elimination of other immune responses [36].

Previous studies have shown several pro-tumor neutrophil mechanisms originate by neutrophils to achieve pro-tumor activities, including the production of CXCR2 chemokines from tumor cells, immune cells, and cancer-associated fibroblasts [38], which mobilize neutrophils through a positive chemotactic
gradient into the tumor microenvironment towards the CXCR2 ligands [34].

Interleukin 17 (IL17), a pro-inflammatory cytokine released by T helper 17 cells, has also been shown to regulate the expression of different cytokines and chemokines, including G-CSF [39]. It was found that G-CSF down-regulates the expression of CXCR4 and converting neutrophils to the N2 phenotype resulting in neutrophil proliferation improvement, maturation, and migration, moreover induces an immunosuppressive tumor microenvironment through high expression and CCL2 secretion, CCL5, neutrophil elastase (NE), and cathepsin G (CG) [40]. Cathepsin G is a peptidase secreted from neutrophil azurophilic granules that stimulate angiogenesis, tumor cell migration, and then induces cell adhesion, forming tumor mass [41].

One of the mechanisms of neutrophil killing of cancer cells is thought to be the production of ROS by neutrophils, and contrary many consider it one of the factors promoting cancer growth [41]. ROS stabilizes HIF-1 alpha, which promotes the development of VEGF (vascular endothelial growth factor) that encourages cancer progression and resistance to chemotherapy [42].

The presence of immature neutrophils and a high neutrophil-to-lymphocyte ratio, in the peripheral circulation, are biomarkers of worse prognosis and lower overall survival in various cancers [43].

Other studies have stated that neutrophils have the ability to eliminate the tumor cells directly through various mechanisms, including the secretion of H2O2 after physical contact with cancer cells, which promotes apoptosis of cancer cells by triggering the interaction of Fas ligand / Fas [44]. It has also been shown that ROS produced by neutrophils, via direct membrane oxidation by HOCl, can induce tumor cell lysis, or through a mechanism similar to that used by NK cells through the secretion of cytolytic enzymes such as perforin and granzyme [45].

The subtype of N1 neutrophils is responsible for anti-tumor activity through immuno-activating chemokine and cytokine expressions, including TNF (tumor necrosis factor) alpha and ICAM-1 [34].

As a therapeutic target, neutrophil elimination in cancer murine models has been shown to decrease tumor mass and metastasis. CXCL6, a chemoattractant for neutrophilic granulocytes, is attacked in the melanoma mouse model by specific anti-CXCL6 monoclonal antibodies, decreasing the number of TANs and the size of the tumor [35].

6) Innate lymphoid cells (ILCs)

Innate lymphoid cells (ILCs) are heterogeneous groups of innate immune cells that belong to the lymphoid lineage but do not respond in an antigen-specific way because they lack a B or T cell receptor [46].

Based on the produced cytokines, ILCs can be divided into ILC1s, ILC2s, and ILC3s that mirror CD4+ T helper (Th)1, Th2, and Th17 cells, respectively, in terms of function. Moreover, the transcription factors can control their function [47].

Group 1 ILCs include cells such as ILC1s, NK cells, intra-epithelial ILC1s, and ILC1 like cells. ILC1s are feebly cytotoxic cells producing type 1 cytokines (Interferon γ and TNF), GM-CSF (Granulocyte-Macrophage Colony-Stimulating-Factor), granzyme and perforin [47]. They collaborate with Th1 cells against intracellular microorganisms that activate macrophages that produce direct cytotoxicity to cancer cells [48].

ILC2s (also called natural helper cells or innate helper 2 cells) have an essential role in type 2 cytokines secretion (e.g. IL4, IL5, IL9, IL13 and amphiregulin). Group 2 ILCs develop an immune response against parasites and allergens and facilitate the repair of tissue damage through their production of amphiregulin [49].

Group 3 ILCs are characterized by their ability to produce IL17A, IL22 and Tumor Necrosis Factor alpha (TNF alpha) cytokines. They include ILC3s and lymphoid tissue inducer (LTI) [49]. They are mainly involved in the immune response against the extracellular microorganisms such as fungi, bacteria and viruses [50].

ILCs can produce anti-tumor functions and induce apoptosis or cell lysis of tumor and virally infected cells. Their function is regulated by the expression of several cell surface receptors that can recognize stressed cells. NKG2D, for instance, is a receptor expressed on natural killer (NK) cells and NK1 that can recognize ULBP and MICA, two surface markers...
that are frequently upregulated in tumor cells [50, 51].

Furthermore, ILC2s and ILC3s can trigger an anti-tumor immune response and promote the leukocyte tumor invasion, inducing tumor cell lysis that associated with a good prognosis. ILC1s, on the other hand, have been shown to have cytokine-dependent anti-apoptotic functions in response to TGF-β or IL-12, promoting tumor growth [51].

7) NK cells

Natural killer (NK) cells are a variety of innate lymphoid cells (ILCs) type I that have a crucial role in the immunosurveillance of cancer cells. They can recognize cells that are abnormally stressed and lacking Major Histocompatibility Complex (MHCs) and able to eliminate tumor cells in vitro without prior sensitization through recognition of non-specialized surface adhesion molecules or antigenic peptides [10, 52]. As early experiments indicated that perforin production by NK cells protected mice from methylcolanthrene (MCA)-induced sarcomas, many transplanted cancer cells are rejected in an NK-cell-dependent way that is not MCH-dependent [53]. Either by selectively enhancing cytokine-dependent NK cell activity, preserving their in vivo survival and proliferation, or by mediating NK cell cytotoxicity, many approaches improve NK cell-based anti-tumor immune functions [54].

Several cytokines, such as IL-2, IL-12, IL-15, IL-18, IL-21 and IFN- α/β, increase the anti-tumor role of NK cells and encourage the proliferation and maturation of NK cells. Experimentally, the administration of these cytokines often increases the immunosurveillance activity of NK cells against the cancer cells [55].

The direct killing by NK cells is mediated by the release of perforins and granzymes leading to cancer cell lysis and apoptosis, through the upregulation of death receptors and by the secretion of different effectors such as INF-γ [56]. The release of these cytokines is associated with the development of nitric oxide (NO) that targets NK cells to kill cancer cells by the NO signaling pathway or by expressing CD16 to destroy cells via antibody-dependent cell-mediated cytotoxicity (ADCC) [57].

In cancer patients, NK cell invasion into the tumor microenvironment is correlated with favorable prognoses, and therapies aimed at improving the anti-tumor activity of NK. [58].

NK-cell-based studies have been developed to achieve significant benefits in the treatment of cancer. Autologous transfusion of NK cells extended ex vivo to treat patients with lymphoma and different solid tumors showed very small antitumor effect because of the activation of the inhibitory signals pathway due to self-recognition of MCH class I on cancer cells [59, 60]. In conjunction with NK cells, immune-stimulating molecules such as antibodies and cytokines are also used in clinical trials to achieve greater tumor-killing activity of transferred NK cells [61].

CAR-NK are another modality of NK-based therapy cells that primarily consist of extracellular, hinge, transmembrane and intracellular domains attached to NK cells [62,63]. Specifically, the extracellular domain can bind to tumor-associated antigens expressed on cancer cell surfaces. While CAR-NK treatment is still under clinical evaluation, preclinical trials have shown positive outcomes. [64,65].

Recently, growing evidence has shown that extracellular vesicles (EVs) released by NK cells carry proteins and microRNAs (miRs) capable of producing an anti-tumor effect, even within a highly immune-suppressive tumor microenvironment [66].

Extracellular vesicles are tiny, nanometer-sized vesicles. With a lipid bilayer membrane, there are three types of vesicles classified according to their size. The smallest membrane vesicles (40-100 nm), microvesicles that bud out of the plasma membrane (50 nm-1μm), and the apoptotic bodies (50 nm-5μm) that formed from cells undergoing apoptosis [54].

Advantages of EVs are; the ability to diffuse through tissues passively because of their nano-size [67], the acidic environment of solid tumors caused by hypoxia-ischemia, promote the fusion between EVs and tumor cells, [68,69] and their ability to traverse biological barriers such as the blood-brain barrier (BBB) and the blood-tumor barrier (BTB) [70, 71].

The ability of EVs to passively migrate through tissues due to their nano-size is of a great advantage that facilitates their movements across the biological membranes such as the blood-brain barrier (BBB) and the blood-tumor barrier (BTB) [67]. Moreover, the acidic environment of solid tumors caused by
hypoxia-ischemia gives the ability to combine EVs with tumor cells [72, 73].

8) Gamma/delta T cells

Numerous studies have shown a role for other innate lymphocyte populations in tumor surveillance such as Gamma/delta (γδ) T cells. Gamma/delta T cells are another class of cytolytic ILCs that can lyse cancer cells. γδ T cells have been shown to limit the incidence of tumorigenesis in models of carcinogen-induced skin cancer and a transgenic prostate adenocarcinoma model [72, 73].

γδ T cells are T cells that have on their surface a characteristic T-cell receptor (TCR). Most T cells are alpha-beta T cells with TCR comprising two chains of glycoproteins called alpha (alpha) and beta (beta) TCR chains. In comparison, γδ T cells have a TCR which consists of one chain of γ (gamma) and one chain of δ (delta). They are called the ‘first line of defense,’ regulatory cells,’ or’ bridge between innate and adaptive responses [74].

Numerous cytokines, including IFN-γ, TNF-α, and extensive chemokines, are also active producers of activated NK cells and γδ T cells. In particular, IFN-γ is known to have important antitumor activities, such as inducing expression of MHC I and sensitizing tumor cells to the cytotoxic CD8+ T-cells. The combination of IFN-γ and TNF-α can also lead tumor cells to apoptosis [75].

CONCLUSION

There is a crucial role for the innate immune cells in immune surveillance through direct defense against cancer cells or via activation of adaptive immunity. In response, the tumor cell changes its immunogenicity to escape immune surveillance. Innate immune cells differ in their activity toward tumors. The Majority has anti-tumor activity as dendritic cells, ILC1s, NK, and Gamma/delta (γδ) T cells that play a crucial role in immunosurveillance of cancer. Others have pro-tumor activities that encourage tumor development, as tumor-associated macrophages and myeloid-derived suppressive cells that involve in tumor cell evolvement, survival and growth. There are innate immune cells that are still ambiguous in terms of anti- and pro-tumor properties like tumor-associated neutrophils and mast cells. A good understanding of the innate immune cells’

activity contributes to increasing the effectiveness of immunotherapy.

References


30- Rajput AB, Turbin DA, Cheang MC, Voduc DK, Leung S, Gelmon KA, et al. Stromal...


