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PROSPECTS

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Role of immune system in tumor progression and carcinogenesis

Shishir Upadhyay[1] | **Nidhi Sharma**[1] | **Kunj Bihari Gupta**[2] | **Monisha Dhiman**[2]

[1] Department of Animal Sciences, School of Basic and Applied Sciences, Central University of Punjab, Bathinda, Punjab, India

[2] Department of Biochemistry and Microbial Sciences, School of Basic and Applied Sciences, Central University of Punjab, Bathinda, Punjab, India

Correspondence
Monisha Dhiman, PhD, Department of Biochemistry and Microbial Sciences, School of Basic and Applied Sciences, Central University of Punjab, Bathinda 151 001, Punjab, India.
Email: monisha.dhiman@gmail.com; monisha.dhiman@cup.edu.in

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Abstract

Tumor micro-environment has potential to customize the behavior of the immune cell according to their need. In immune-eliminating phase, immune cells eliminate transformed cells but after tumor establishment innate and adaptive immune cells synergistically provide shelter as well as fulfill their requirement that helps in progression. In between eliminating and establishment phase, equilibrium and escaping phase regulate the immune cells response. During immune-escaping, (1) the antigenic response generated is either inadequate, or focused entirely on tolerance, and (2) immune response generated is specific and effective, but the tumor skips immune recognition. In this review, we are discussing the critical role of immune cells and their cytokines before and after the establishment of tumor which might play a critical role during immunotherapy.

KEYWORDS

adoptive T cell transfer, chemokines, cytokines, immune surveillance, micro-environment

1 | INTRODUCTION

Tumor or cancer arises from a series of auto-unregulated intracellular (eg, apoptosis) or intercellular (immune) mechanisms. A tumor is not a single step consequence; it is an evolutionary process that alleviates the cells for any such circumstances. Besides being benign or malignant, a tumor can be contagious too such as in Devil Facial Tumor Disease (DFTD) in Tasmanian devils and CTVT (Canine Transmissible Venereal Tumor).[1] Hanahan and Weinberg[2] explored various characteristics of cancer such as angiogenesis, metastasis and evasion of apoptosis, inflammation, senescence, and immune-escaping.

The role of immune cells and associated factors seems paradoxical in tumor milieu. The investigations articulated that tumor not only crafts a shield for itself, but its exploitation of immune system and other killing factors (eg, inflammation) add to the audacious malignancy, angiogenesis and many other processes that support their growth. Ideally, the immune system should respond by eradicating the tumor and should maintain homeostasis. However, genome plasticity in some tumor cells enables them to proliferate continuously thereby, establishing an equilibrium phase with the host by escaping the immune attack to install a clinically detectable tumor followed by metastasis.[3] Immuno-escaping, in context to tumor, relates with either immunosuppression or immune-corporation that involves taking help of immune cells for further progression of cancer. After establishment of tumor, stromal as well as the tumor cell itself modulate the activity of immune cells (being infiltrated during inflammation) that afterward, induces angiogenesis, metastasis, invasion, and intravasation and suppress antitumor response. The chemokine-regulated immune cells are first recruited, cultivated but then, utilized by the tumor micro-environment for its own progression[1,4] the mechanism is still not clear. According to a proposed tactic for immune-escaping, HLAs (Human Leukocyte Antigens) expressed by tumor affects its interaction with host immune

system, which is thought to play an important role. Suppression of the innate and/or adaptive immune response by non-classical HLA-G is among the most potent escape feature, also witnessed in lung cancer.[5] In present review, we shall try to summarize the immune factors and other associated anomalous behavior as protagonists for immune-editing and immune-escaping features in the tumor dilemma.

2 | IMMUNITY AND TUMOR ANTIGENS

The tumor antigens are differentiated as tumor associated or tumor specific antigens based on the fact that either they are present on normal or tumor cells, respectively. Tumor-specific antigens, expressed exclusively by tumors, arise from mutations or translocations of normal cellular genes (eg, β-catenin, CDK4, Ras) or from overexpression of some proteins (eg, p53, HER2 (human epidermal growth factor receptor 2) viral antigens (eg, human papilloma virus (HPV) E6 and E7 proteins).[6,7] For targeted destruction by distinctive branches of immune system, the antigens are processed and presented along with MHC (Major Histocompatibility) molecules on the surface of various APCs (Antigen Presenting Cells) such as, dendritic cells, activated macrophages, and B cells. The tumor neoantigens scavenged by APCs are cross-presented to the adaptive immune system.

At times, these antigens can escape from immune cells either by inefficient stimulation of innate/adaptive immune responses or by antigen tolerance. The escape from adaptive immune response is accomplished by impaired antigen presentation. Expression of the tumor antigen such as Human leucocyte antigen (HLA), downregulation, or upregulation leads to enhanced tumor incidence and metastasis.[8] Moreover, the mutation of the antigen can result in escape from initial response and contribute to heterogeneity of tumor lesions. Heterogeneous expression of multiple antigens may also hinder the establishment of an efficient specific immune response. Tumor cells generally show downregulation of MHC-1 with unrecognized mechanism, hinders the T cells-mediated immune responses in many tumors such as breast, pancreatic, prostate, and bladder[9–12] but theoretically becomes more susceptible for natural killer (NK) cell lysis. Although, survival contrivance such as positive expression of less polymorphic HLA-E providing protection against reactive NK cells lysis has been reported in gynecological cancer and colorectal cancer.[13,14] Further, the mutation of β-2 microglobulin subunit or Transporter associated with antigen processing (TAP) protein might reduce the expression of MHC-1 that can prevent the recognition of tumor cells by NK cells.[6] According to Algarra et al,[15] MHC class I negative metastatic colonies are produced in immunocompetent animals, and MHC class I positive colonies in T-cell immunodeficient individuals. Downregulation of adhesion molecules in malignant tissues may inhibit immune infiltration and in this way, causes immunological ignorance.[6]

Other than HLA, some additional antigens also encourage the tumor metastasis for example, Mucin in ovarian and breast carcinoma,[16] MART1/melan, preferentially expressed antigen in melanoma (PRAME), Melanoma antigen genes (MAGE and GAGE) has been associated with metastatic melanoma,[12,17] and Tumor associated antigen (TAA) are expressed in neuroblastoma tumors.[18]

3 | INNATE AND ADAPTIVE IMMUNE RESPONSES DURING TUMORIGENESIS

Innate and adaptive immune responses of the body cross-talks and shows immune-surveillance for cancer cells. In addition, infiltrate in the tumor stroma itself too carries several types of immune cells. Macrophages, neutrophils, dendritic cells, and other participating cells of innate immunity are the major components of leukocyte tumor-infiltrate. A Recent study on mice and human have reported that a sensing mechanism in host innate system, the STING (Stimulator of interferon genes) pathway involves in driving force in activating a major innate immune for detecting antigens in growing tumor and T cells priming through the production of type 1 IFN.[19] The innate immune response keeps checking on cancer by direct killing of tumor cells, by destruction of tumor vessels or matrix and by inhibition of angiogenesis. Though the prime goal is to eliminate tumor cells yet the same is manipulated by tumor for its own welfare. It is likely that the immune cells in micro-environment are clueless about the identification of tumor specific antigens, or defense system shows failures. Two situations are possible: (1) the antigenic response generated is either inadequate, or focused entirely on tolerance, and (2) immune response generated is specific and effective, but the tumor skips immune recognition.[13] Once the immune response fails somehow, tumor developing its micro-environment flourishes by customizing various immune cells. Various branches of the two types of immune response, their cross talks and their role in tumorigenesis will be discussed in detail further. B and T cells are the major effectors of adaptive immunity. While it is quite clear that the acute activation of B cells might be involved in eradicating early neoplastic cells or in spontaneous tumor regression through classical and well-studied antibody-mediated mechanisms. But recent reports have indicated that chronic activation of B cells might encourage carcinoma development in a complex manner.[20] The adaptive immune responses may also cause: (1) ongoing and excessive activation of the innate system; (2) antibody deposition in tissues resulting in recruitment of innate immune cells; and (3) T lymphocyte dysfunction instead of activation. The reversal in the roles

between the non-specific and specific systems has also been reported during chronic inflammation in tumor niche.[21]

Broadly speaking, cells that may sustain to escape mechanism are: (1) regulatory dendritic cells- create tolerance to the antigen being presented by dendritic cells[22]; (2) T regulatory (T_{reg}) or suppressor T cells propagate antigenic tolerance[23]; and (3) Myeloid-derived suppressor cells (MDSCs), a family of varying subtypes including the ones which secrete pro-inflammatory factors supporting angiogenesis, invasion, and metastasis deliberated as important immunological hallmarks of cancer.[24–26]

3.1 | Natural killer cells

An essential part of innate immunity, natural killer (NK) cells are cytotoxic lymphocytes. Different from a typical immune cell, NK cells are unique as they can spot the infected cells without requiring antibodies or MHC, providing a rapid response in case of virally infected cells and tumor formation. These cells are the initial cellular response against dissemination of blood borne metastasis and also extravagate and destroy solid tissues to inhibit metastasis and are activated by IL (Interleukin)-2.[27] These cells have destruction ability against TRAIL (TNF-related apoptosis-inducing ligand) sensitive, MHC-1, and NKG2D associated cancer cells by either by releasing perforin, granzymes, chemokines (IFNγ, TNFα, and GM-CSF), or by activating the adaptive immune response by expressing KIRs (Killer Immunoglobulin Receptors).[28,29] IFN-γ (Interferon-γ), for instance, contributes to the antitumor control directly by inhibiting proliferation/metastasis and indirectly by inducing antiangiogenic factors (IP-10), IL-12, and enhancing cytotoxicity or by recruiting dendritic and T effector cells mediated response.[28,30] The ability of IL-15 and IL-15Rα expression that imparts control over solid tumors had also been seen in micro-environment of mouse models and is predominantly mediated by NK cells.[31] Eliciting the FcγRIII (CD16) response can allow NK cells to maintain their killing capability through alternate approach of antibody-dependent cell cytotoxicity (ADCC).[32] In mice, a shed form of MULT1, a high-affinity NKG2D ligand, causes NK cell activation and tumor rejection.[33] In neuroblastoma cells, NK cells can contribute to antitumor effects by prompting the MHC-I up regulation[34] hence playing an important role in tumor eradication. Two other subsets of NK cells- CD56 ^{dim} $CD16^{+}$ and CD56 ^{bright} CD16 low cells, often present in peripheral blood stream, display high and low cytotoxic effects, respectively. In an in vitro study on melanoma cells, it has been found that IL-2 or IFN-α induces the NKG2D and CD161 NK cell receptor expression on $CD3^{-/-}$ $CD\ 16^{+}$ NK cells and enhances cytotoxicity against tumors.[35]

Virus infected and transformed cells generally lack or have lesser self-major histocompatibility complex—class I (MHC-1) molecules. These cells with the "missing-self" do not get identified or destroyed by other immune cells, act as targets for the NK cells.[35] In addition, heat shock protein-70 (Hsp70) and the stress-regulated MICA/B (MHC-1 Chain-related Protein A and B) both serve as ligands for activated NK cells when expressed on tumor cell surface. Despite their killing action toward tumor, sometimes under selective pressures, certain mutations in cancer cells helps them to evade NK cells surveillance. How NK cells become less functional in tumor is not well understood. But, evidence is persuasive that the down-regulation of the subunits-β-2m, LMP-2, and LMP-7 (low molecular mass polypeptide) modifies the peptide spectrum of MHC-1 molecule. The protein involved in loading antigenic peptide on to MHC-1 is a transporter associated with antigen processing (TAP), TAP-associated protein Tapasin is also frequently mutated or down-regulated in tumors. TAP deficiency result in loss of MHC-1 expression and increase in tumorigenesis.[36] Similarly, recent investigations in Head and Neck Squamous Cell Carcinoma (HNSCC) patients has given compelling evidence that soluble major histocompatibility complex Class I chain-related peptide A (sMICA) along with chemokines TGF-β1 responsible for NK anergy through impairments in NKG2D.[37] Conclusively, altering the MHC-1 expression offers an escape from NK cell-mediated lysis.

According to "discontinuity theory of immunity" NK cells having ability to sense the changes from self to non-self, yet a continuous exposure of altered self-antigens or tumor antigens makes it anergic in response. In developing tumor, NK cells usually drive the macrophage/T cells to acquire antitumor activity but after the establishment of tumor, these cells act as tumor-promoting and shows no interaction with NK cells that suppress the NK-mediated cytolytic response.[38] In some contagious cancer (CTVT and DFTD), the affected cells loose MHC from their surface and also release chemokines (eg, TGF-β) which are suspected to suppress the NK cells activity.[1]

The dysfunctional NK cells in myeloma is generally associated with low expression of CD161, activating NKG2D receptors, $CD16^{bright}$ and less NK-cell interferon (IFN-γ) production, with increase $CD16^{dim}$ independent of increase in killer cell Ig-like receptors (KIR) receptors.[39,40] In tumor vicinity, the activity of NK cells is also comprehended to be down-regulated due to immune suppressors produced by tumor cells.[35] Cancer biologists have postulated that tumor cells release some chemokines such as corticosteroids, indoleamine 2,3-dioxygenase (IDO) and prostaglandin E2 (PGE-2), are responsible for anergy of NK cells.[41] Interestingly, the activating NK receptors inhibited by IDO and PGE2 are functionally counteracted by NKG2A, an inhibitory receptor utilized by both T and NK cells. Like IDO and PGE2, in the NKG2A inhibitory ligand, HLA-E is expressed and functional in tumor cells, including melanoma and colorectal carcinoma.[41,42] It is thought that tumor cells

evade immune surveillance by shedding membrane ligands that bind to the NKG2D-activating receptor on NK cells and/or T cells, and desensitize these cells. But it is not clearly elucidated that how this will further help in tumor metastasis and development. Researchers also reviewed that immune-evasion requires simultaneous derangement of both T and NK cells, as shown by the analysis of MHC-I phenotypes of human tumors.[41] Further investigation showed that HLA-G and HLA-E indirectly inhibits CD25 + T cells activation by shutting down the NK cells migration and IFN-gamma secretion.[43,44]

Hypoxia, one of the characteristic feature of tumor micro-environment contributes to the evasion from NK cell-mediated cytotoxicity by downregulating the mainly IL-2 or some other cytokines IL-15, IL-12, and IL-21 induce activating NK-cell receptors (NKp46, NKp30, NKp44, and NKG2D), and increase the intracellular level of perforin and granzyme B but has no effects on NK cell ligands (HLA-ABC and −E, MICA/B, and ULBP1-2) and receptors KIR, NKG2A/C, DNAX accessory molecule-1 (DNAM-1), natural cytotoxicity receptors (NCR), and 2B4. In hypoxic conditions, recruited T_{reg} cells produces TGF-β, responsible for anergy NK cells.[32] In addition, hypoxic stress can induce the formation of dimers of the non-classical MHC class I molecule HLA-G at the surface of melanoma cells, thereby protecting tumor cells from NK-mediated killing. It appears that such induction is mediated by secretion of IFN-β and IFN-γ and by direct interaction of HLA-G with NK cells (Figure 1).

3.2 | Macrophages

Macrophages are known for their genome plasticity and variability as per micro-environment conditions. Macrophages (M1) arise from monocyte-derived lineage and show antibody-dependent cell mediated cytotoxicity (ADCC), another tumoricidal activity. During immune-surveillance, they also secrete a range of cytotoxic factors such as reactive oxygen species (ROS) and reactive nitrogen species (RNS), tumor necrosis factor (TNF), etc. RNS-nitric oxide (NO) and polyamines are generated by iNOS (inducible NO synthase) and arginase enzymes activity during the tumoricidal action of macrophages.[45] Thrombospondin, a glycoprotein generally produced by platelets and macrophages that drive M1 macrophages, is tumoricidal. M1 macrophages are the effectors of pro-inflammatory response and stimulate T_H1 responses while M2 macrophages or Tumor-Associated Macrophages (TAMs) is anti-inflammatory and pro-tumorigenic in nature. They inhibit tumor proliferation by releasing cytotoxins (ROS), degradable enzymes (serine proteases) and cell-lysis factors as well as engaging T cells through processing and presenting of tumor antigen.[46] M2 macrophages mediate inflammation and adaptive type I immunity, clear debris, promote angiogenesis, tissue remodeling, and repair. M2 cells produce anti-inflammatory cytokines (IL-1, TNF, and IL-6)[47] with low IL-12 and high IL-10 profile and poor antigen-presenting capacity, suppress the T_H1 adaptive immunity.[48] Some experimental evidence also support the facts such as Inhibition of IKK-β (Inhibitor of Nuclear Factor Kappa-B Kinase subunit beta) in TAMs guides the polarity of macrophages from M2 toward M1 phenotypes, which actively kill tumor cells[49] (Figure 2).

Macrophages (M2) and other myeloid cells are universally found in the solid tumor microenvironment and can contribute to immune evasion. Myeloid-derived suppressor cells are immature myeloid-lineage cells that can be immunosuppressive in tumor micro-environment.[31] M2 macrophages, in micro-environment, secrete many factors-PDGF (Platelet-derived Growth Factor), human angiogenic factor (HAF), angiotropin, chemokines (CXCL8 or IL-8), and Semaphorin 4D (CD100) that assist in tumor propagation in one way or the other.[50,51] The interacting tumor micro-environment is found to constitute majorly of M2 macrophages and immature dendritic cells that induce T cell anergy through the activation response mediated by CCL18. Chemokines regulate the production of CCL-18 from immature dendritic cells and macrophages, and of IL-10 from tumor cells. Again, the IL-10 helps in differentiation of monocytes into mature macrophages, instead of dendritic

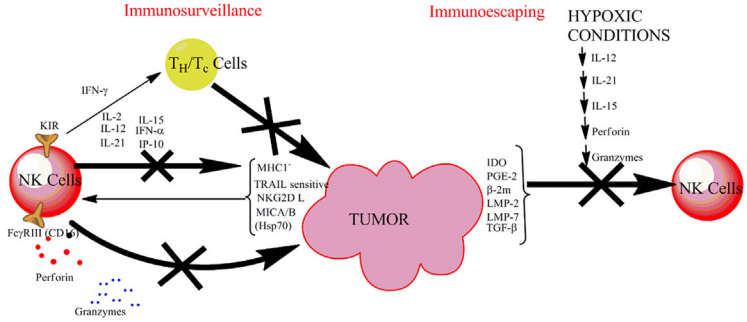

FIGURE 1 NK cells in tumor micro-environment. During Immuno-surveillance, NK cells target the tumor and destroy directly or indirectly by activating adaptive immune response. In immunoescaping, Tumor and hypoxic micro-environments, anergise NK cells by releasing cytokines

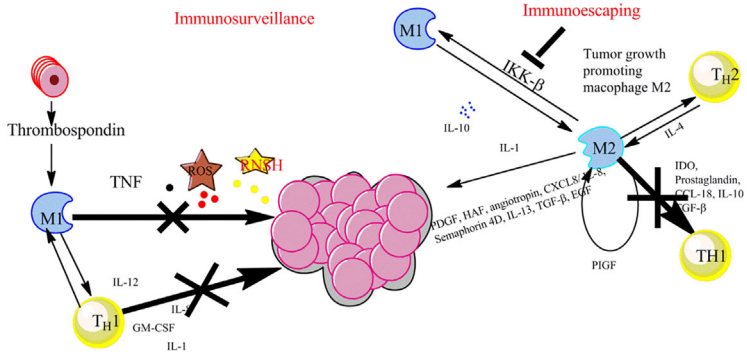

FIGURE 2 Tumor micro-environment and macrophages. Macrophage (TAM) plasticity according to different stage of tumor. In Immunosurveillance, M1 destroy tumor cells directly by generating ROS, RNS, and different Chemokines. M1 also activates adaptive immune response through T_H1 cells. In immune-escaping, M2 promotes tumor evasion by releasing growth factors and by inhibiting T_H1 response and by activating the T_H2 response

cells, by M2c pathway of macrophage activation and prompts TAMs to express M2 related functions.[52] Unlike M1, M2 macrophages lack cytotoxic action and are potent tumor-promoting entities and appear to contribute to immune suppression through the production of IL-10 and TGF-β and promotes tumor through representation of arginase-I, scavenger and mannose receptors, vascular endothelial growth factor (VEGF), matrix metalloproteinases (MMPs), osteopontin.[53] M2 suppress T-cell activation and proliferation through the release of prostaglandins, IL-10, TGF-β, and IDO (a tryptophan catabolizing enzyme). Unable to trigger T_H1 response, T_{reg} are stimulated through production of CCL22 further inhibiting T effector cells. Also, the cathepsin protease activity felicitated by IL-4 in these macrophages promote cancer growth and invasion.[54] Thus, M2 macrophages are likely to be produced during macrophage differentiation in this environment. Their production is also promoted by IL-4, IL-13, IL-10, and M-CSF. M2 also encourage metastasis mediating through MCP-1/CCL2 and stimulating the macrophages to secrete urokinase-type plasminogen activator (uPAR) and MMP-9, both of which have the ability to remodel the tumor ECM.[53] IL-4 produced by tumor-infiltrating CD25+ T_H2 cells skews the TAM into a metastasis-promoting population thus producing high levels of Epidermal Growth Factor (EGF).[55] Conclusively, M2 cells are major hinderance for adaptive mediated immune response through T cells and also secrets major cytokines that help in tumor progression.

TAMs are found in stroma of many tumors and can affect several other aspects of neoplastic tissues. They act as prime mediators of inflammation. Chronic inflammation is yet another cancer characteristic. The placenta growth factor (PGF) released during chronic inflammation in tumor supports the survivability of TAM. The Higher profile of TAMs and their stimulatory factors such as, chemokines and cytokines (CSF-1,CCL2, IL-10, TGF-β) parallels with poor diagnosis and increased cancer incidence of bladder, breast, and cervical tissues.[56]

The presence of TAMs near blood vessels is a boon for disease progression as they attract cancer cells. Directed by their movement, the extravasation of cancer cells occur only in the vicinity of the macrophages. Such a three-way communication between invasive cancer, macrophages, and endothelial cells is termed as Tumor Micro-environment of Metastasis (TMEM) forms the basis to trace distant metastasis in cancer for example, breast cancer.[55] However, clinical studies have shown that a higher number of intra-tumor macrophages correspond to high vessel density and tumor progression. In an experiment on stem cells, TAMs were not only found to be tumorigenic, besides they enabled the tumor to modulate antitumor drugs. The drug resistance is arbitrated by synergistic effects of MFG-8 and IL-6 secreted by TAMs.[57]

3.3 | Neutrophils

Just like the macrophages, neutrophils show plasticity during patho-physiological conditions and can have distinct phenotypic and functional profiles. Neutrophils regulate the function of innate and adaptive immune system in various inflammatory diseases like cancer, through releasing of different cytokines and effectors molecules.[58,59] The inflammatory environment is also responsible for inducing novel chemokine receptor repertoire on recruited infiltrating neutrophils, which impairs its functional response to surrounding chemokines such as, CCR7, CXCR3, and CXCR4 and high levels of CCR 5.[60] Hereby, two kinds of neutrophils can be usually found that are categorized as- TEN or the tumor entrained neutrophils, and TAN or the Tumor-associated neutrophils. TEN displays anti-metastatic characteristics while, TAN exerts pro-tumorigenic effect within the same micro-environment by suppressing immune responses and promoting angiogenesis.[61]

In early tumors, TEN (N1) were noticed to be more cytotoxic toward tumor by secreting higher levels of TNF-α, NO, and H_2O_2 and activating T cells and acquire anti-metastatic properties by secreting CCL2.[60,62] While in established tumor, TAN participates in ECM (extracellular matrix) remodeling, cancer cell invasion, metastasis, proliferation, and lymph angiogenesis and inhibits the anti-tumoral immune surveillance.[62] The infiltrating TANs are driven by TGF-β to acquire a pro-tumoral N2 phenotype. As a result, the TGF-β inhibition induces an anti-tumoral N1 phenotype.[63] TAN also flourishing the tumor through MMP-9, CXCL1, TNFα, and growth factors FGF, HGF, EGF, and VEGF-mediated angiogenesis. During this course, some other chemokines are also secreted IL-8/CXCL8, MIP-1/CCL3, HGCP-2 (hu GCP-2/CXCL6), IL-1, IL-2, IL-4, IL-7, IL-10, and IL-12 that favors the enhanced survivability and recruitments of N2 neutrophil.[60,64] Recently, the prognostic role of TAN has been associated with poor clinical outcome in several human cancers, most notably in renal cell carcinoma (RCC), melanoma, colorectal cancer (CRC), hepatocellular carcinoma (HCC), intrahepatic cholangiocarcinoma (ICC), gastric, pancreatic ductal carcinoma (PDC), and head and neck cancer (HNC).[60,65] Metastatic primary tumor-infiltrating Th17 lymphocytes predominantly recruiting N2 cells by elevating cytokines IL-17 in micro-environments, further adding up the negative role in tumor escaping.[64]

Besides the above stated, neutrophil bolsters tumorigenesis by uptake of elastase, and by hydrolysis of insulin receptor substrate-1 (IRS-1) subsequently resulting into enhanced levels of PDGFR signaling and tumor cell proliferation.[66] Interestingly, it can also modify the tumor suppressor role of some ECM components, as has been reported for Elastin Microfibril Interfacer 1 (EMILIN1) that is cleaved by neutrophil elastase into inactive fragments. This proteolysis consequently impairs its anti-proliferative mode.[67]

3.4 | Dendritic cells

Dendritic cells present antigens to T cells, and are MHC-1 and MHC- 2 restricted. These cells are major sources of cytokines especially, IL-12, IL-3 which can direct both innate and adaptive immunity and favor T_H1 type immune responses in tumor rejection.[68] IL-12 secreted by host dendritic cells brings about Tc17 plasticity and antitumor activity.[69] In the presence of IFN-α mature dendritic cells shows efficiency of recognition and acts as T cells.[70] Tumor-infiltrating dendritic cells (TIDCs) trigger TGF-β production, which is well recognized for extricating the tumors through T-cell mediated signaling.[68] On the other hand in certain cases, TIDCs either fail to present tumor antigen properly to CD25 + T cells,[71] or impede pro-inflammatory response by stimulating inflammatory T_H2 (iT_H2) cells once the tumor is established.[72] Investigations also reported that in tumor micro-environments, a pro-inflammatory cytokine- PGE-2 stimulates the production of IL-10 either from tumor itself or infiltrated leukocytes, which in turn inhibit the recruitment and accumulation of dendritic cells.[68,69] Both PGE-2 and IL-10 further decrease the IL-12 secretion by dendritic cells and consequently, lowering the immune responses. Thus, immunosuppression by tumor affects activation of dendritic cells by T_{reg} cells and also influences the interaction with T effector cells.[73] A tumor derived ganglioside is also known to lessen the number of dendritic cells.[68] These intratumoral dendritic cells can express IDO and PD-L1, which may contribute to their suppressive phenotype, and show defective production of type I interferon.[74] The mechanism by which tumors induce type I interferon production in host dendritic cells bridges the adaptive CD25+ T cell response.[75] The regulatory dendritic cells can also prompt antigenic tolerance and immune suppression by instructing CD25+ T cells via B7 receptor signaling pathway (Figure 3).

3.5 | T cells

T cells like other immune cells also show diverted role in tumor micro-environment. T cells are classified into MHC-II restricted CD25+ (T_H1/helper T) and MHC-I restricted CD25 + T (Tc/cytotoxic T) cells. The subsets of CD25+, T helper cell type 1 (T_H1), and T helper cell type 2 (T_H2), can activate CD25 + T cells and stimulates humoral immune responses, respectively. The CD25+ T cells show plasticity that is, it can be differentiated into multiple lineages. Generally, during tumor development, T cells are activated by Dendritic cells and recruited to tumor vicinity that further aggrandizes the T cell infiltration lymphocytes (TILs) performance and functioning and provides immune-surveillance.[76] The fact that tumor cells lack MHC-II antigens, Tc cells are considered as a key antitumor component and utilized as a potent immune weapon against tumor in the adoptive T cells therapy.[77] In addition, CD25+ T_H1 cells also eradicate tumor cells through activation of Tc and NK cells and by releasing some cytokines such as IFN-γ, TNF-α, Monocyte Chemotactic Protein (MCP-1), or CCL-2, Macrophage Inflammaotry Protein (MIP-1α). However, the roles of Th2 and another subset T_H17 at times, can be contradictory depending on tumor developments and micro-environments. T_H17 subset displayed an indirect antitumor response by recruiting dendritic cells.[78] In tumor, CD25+ T cytotoxic T cells can directly kill tumor targets, after TCR and MHC-I aided recognition of tumor antigens, while CD25+ cells support CD25+ cells and boosts primary immunity in priming phase and effector phase against MHC-II negative tumors.[79] In proliferative stage, NK cells or Tc cells mediates killing of tumor cells in the presence of low levels of suppressive cytokines.[80] T cell infiltration associated with expression of CCL-21 that recruits naïve T cells and activated DCs with

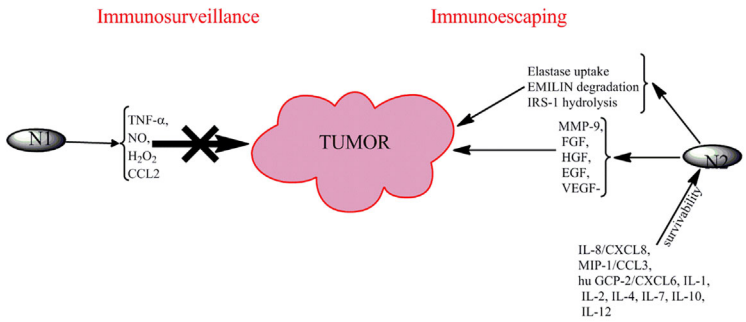

FIGURE 3 Neutrophils in tumor micro-environment. In Immuno-surveillance, Neutrophils (TEN/N1) inhibits tumor by releasing different chemokines, while (TAN/N2) helps in tumor escaping and progression

effector T cells. In Melanoma micro-environment, Tc cells produce CCL-2, CCL-3, CCL-4, CCL-5, CXCL-9, and CXCL-10 that also helps in destroying the tumor. Neo-antigens (point mutation) can further energize antitumors Tc cell responses. These explain why non T-infiltrated tumor cells are reported with less recovery from disease as compared to T-cells infiltrated tumor[81] (Figure 4).

Despite the major T cell mediated antitumor activities, tumors are capable of escaping T cells by: (1) directly or indirectly inhibiting T cell accumulation; (2) spreading of tumor cells irrespective of immune-surveillance; and (3) tolerance or avoidance from T cells. At first hand, the T-cell infiltration to the micro-environment is restricted by fibroblast and collagen deposition that obstruct the effectors T cell-encounter with tumor cells. The expression and functional activities of arginase and nitrosylation of surface proteins are known to impede the effector T cells in immature myeloid lineage cells.[81] In fact some inhibitory factors extracted from TILs exert reciprocal effects on T effector cells such as TIM3 (Mucin Domain-Containing Protein3), LAG3 (Lymphocyte Activation Gene3 Protein), PD1 (Programmed Cell Death Protein 1), and CTLA4 (Cytotoxic T-Lymphocyte Antigen 4).[80] STAT3 signaling in CD25 + T cells inhibits the expression of CXCL-3, (the receptor of chemokine CXCL10) to ablate the efficient accumulation of CD25+ T cells thereby reducing IFNγ level.[82] Tumor infiltration by human T cells is a powerful predictive biomarker of survival for ovarian and colorectal cancers.[80] Cancer cells utilize various mechanisms which help them in avoiding T cell-mediated destruction. One among numerous is the loss of HLA-I expression via loss of β-2m (Beta 2-Microglobulin).[83] Some of the tolerance strategies of cancer against the peripheral T-cells encompass T_{reg} and T cell anergy (as explained in macrophage section), fatigue and senescence, all impairing the ongoing T cell-mediated immunity.[83] PD-L1 (Programmed Death-Ligand 1) is yet another signaling protein which, when forms complex with the PD-1 receptor, sends CD25+ T cells to hibernation. Tumors that express PD-L1 are sometimes seen to be surrounded by a phalanx of impotent T cells that are unable to cast immune response.[84] MDSCs (Myeloid-Derived Suppressor Cells) can induce immunosuppressive activities and tumor promoting factors (VEGF, ARG1, and COX2)[85] (Figure 5).

The expression of several angiogenic factors (including chemokines) appears to be on a higher side in those human tumor subsets that exhibit lesser number of infiltrating T cells.

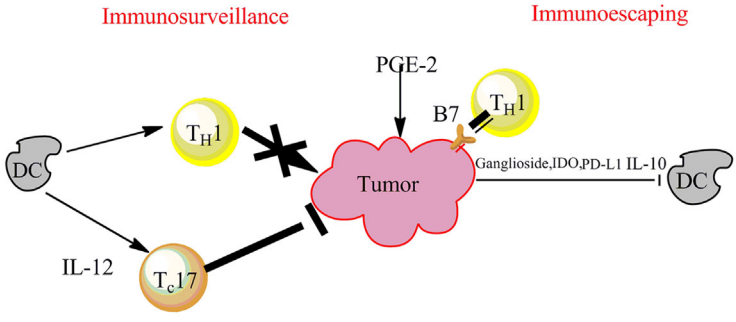

FIGURE 4 Dendritic cells in tumor micro-environment. In immune-surveillance, DC Activates adaptive immune response through T_H1 and T_H17 cells activity and destroy tumor. In Immuno-escaping, Tumor secrets some chemokines inhibits the DC activities. PGE-2 also help in tumor progression

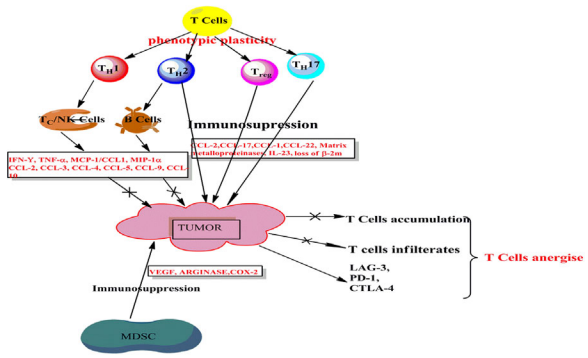

FIGURE 5 T cells in tumor micro-environment. T cells phenotypic plasticity in tumor micro-environment. T_H1 destroy the Tumor cells by utilizing different cytokines and T_H2, T_H17, T_{reg} cells promotes tumor through immunosuppression

NF-kB signaling interceding CCL2 (a T cell chemokine) expression is stated to be associated with enhanced tumor growth in a mouse lung cancer model.[86] Eventually, T_C cells grow to be anergic in tumor vicinity due to: (1) lack of co-stimulatory molecules; (2) presence of cytokines such as, TGF-β and IL-10; and (3) activation of regulatory T (T_{reg}) cells that further suppress the action of T_H1 and CD25+ T cells[31] and inhibit the host antitumor response.[87] That is why, tumor patients with 20-30% increased levels of T_{reg}-CD25+ FOXP3 (Forkhead box P3) have poor survival rate. Another mode of immune-tolerance is the expression of CCL21 in tumors that can probably deactivate an initially recruited naive T cells specific for tumor antigens the process of antigen presentation without proper co-stimulation. T_H17 subset is responsible for angiogenesis and further inducing chemokines CCL-2, CCL-17, CCL-1, CCL-22, matrix metalo-proteinases, IL-23 that leads to a progressive or chronic inflammatory condition. Likewise, the contradictory role of TCR has also been found in different types of cancer for example, T cells expressing TCR (gamma-delta T cell receptor) isolated from breast cancer patients were found to suppress T cell activation in vitro.[88,89] Furthermore, S100A4 molecules of tumor are involved in attracting T cells and stimulate inflammation and responsible for polarization of T_H1 to T_H2 cells and metastasis.[89]

3.6 | Natural killer T cells

Natural Killer T (NKT) cells co-express T as well as NK cell markers, αβ TCR, and NK1.1 (CD161), respectively. The subtypes, NKT 1 and 2, both are CD1d MHC restricted $NK1.1^+$ cells, and referred to as classical (invariant) iNKT and diverse (non-variant) NKT cells, respectively.[90,91] Several antigen presenting cells (APCs) including, dendritic cells, macrophages, B cells, thymocytes, and hepatocytes, that express CD1d molecules can all activate iNKT cells.[92] NKT1 or iNKT cells appear to protect against tumors. In tumor micro-environment, iNKT cells recognize unique lipid antigens on $CD1d^+$ tumor cells and secrete some chemokines such as, IL-12 and IFN-γ to enhance the activities T_H and T_C cells. The decreased frequency of NKT1 cells and deficiency in IFN-γ secretion have been testified in some cancer incidences. Earlier studies on spontaneous and experimental models of mice and human documented the anti-angiogenic and anti-metastatic role of iNKT cells.[91] NKT and NK cells are known to collaborate in host protection from MCA (methylcholanthrene) induced fibrosarcoma.[93] Although there is no direct evidence, so far, to establish that how these cells bridge the gap between innate and adaptive immune response. The regulation of antigen-specific IgE production by NKT cells might be one of the probable answer. Further, NKT cells activated through antigen presented by DC play a pivotal role in initiating T and B cell acquired immunity.[94] The B cells presenting α-Gal-Cer and free α-Gal-Cer make NKT anergise while the DC and B cells encounter with same antigen along with CD1c enhance the ability to activate iNKT cells.[95,96] Thus, vaccination with α-Gal-Cer pulsed DC can activate and expand NKT cells population in human cancer patients is also being evaluated and has shown clinical activity in multiple myelomas.[31] Type-2 NKT cells downregulate the activity of iNKT cells.[97] These cells produce IL-13 which in turn induces TGF-β production by myeloid cells and thus, acts as immunosuppressive in function.[31] NKT10 a naturally occurring subset of NKT cells, functioning similar to T_{reg} cells and produces IL-10 that actively dampening the antitumor response, and may act to promote tumor growth[98] (Figure 6).

4 | CYTOKINES AND CHEMOKINES

Cytokine is a term used collectively for a group of immune-active compounds that include interferons, interleukins, chemokines, and tumor necrosis factors (TNF). Chemokines are classified into four highly conserved groups based on their cysteine position: CXC, CC, C, and CX3C, and regulate cell trafficking.[99,100] There are several examples where chemokines play direct/indirect role in tumor inhibition. The CXCR3-binding chemokines viz., CXCL9, CXCL10, and CXCL11, recruit T_H1 and NK cells to induce anti-tumor activities. Similarly a chemokine, CCL5 not only direct T_H1 and CTLs but monocytes also that can differentiate into TAMs, which in turn increase anti-metastatic activity by promoting the recruitment of CD25+ follicular T_H cells.[101] Furthermore, CXCL4/CXCR3, CXCL14 inhibit endothelial cell chemotaxis; (basic fibroblast growth factor) in vitro and inhibit both (basic fibroblast growth factor) (bFGF) and CXCL8/IL-8 driven angiogenesis in vivo.[102]

In contradiction to their defensive role against tumors, chemokines are generally double-faced in tumor

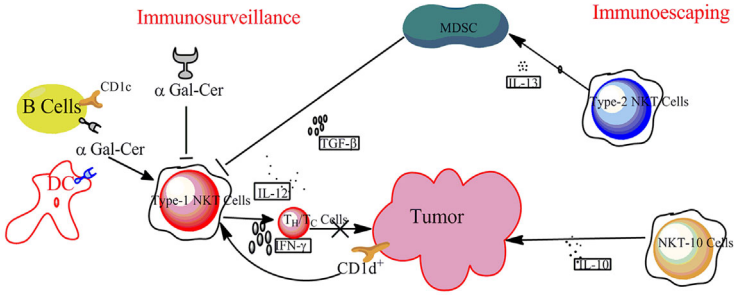

FIGURE 6 NKT cells in tumor micro-environment. During Immuno-surveillance, activated NKT 1 cells play a major role in tumor elimination. In immune-escaping, NKT2, and NKT 10 cells release chemokines and indirectly through MDSC and directly promotes tumor

micro-environment. They contribute right from the initiation to organ-specific metastasis.[103] One well-known chemokine receptor, namely CXCR4/CXCL12, has been reported in progression and metastasis in majority of cancer types such as epithelial, mesenchymal, and haematopoeitic origin.[100,104,105] Overexpression of chemokine 13 (CXCL13)/CXCR-5, in the presence of HIF (Hypoxia Inducible Factor)-1 and TGF-β, promotes malignant progression and metastatic dissemination of prostate, breast, and neuroblastic tumors, NSCLC (Non-small cell lung carcinoma), non-AIDS, and AIDS-Associated Non-Hodgkin's Lymphoma while, its inhibition delayed the tumor.[104–108] Similarly, an adverse role has been noticed for CXCR4, CCR7, and CCL2 in promoting breast cancer[101,102,109,110]; CXCR4, CCR9, and CX3CR1 in prostate cancer progression[110] and CXCR4, CXCR6-CXCL16, and CCR9-CCL25 in lung cancer.[110,111]

Several pathological disorders including tumors are marked by accumulation of leukocytes subpopulation. Chemokines, a major constituent of tumor infiltrate, are involved in adaptation of a tumor in its micro-environment and further by recruiting various types of leucocytes, they embrace tumor growth in terms of survivability, proliferation, and metastasis by creating pro-inflammatory conditions.[112] In Hodgkin's lymphoma, CCL17 (TARC), CCL11 (Eotaxin), and CCL22 (MDC) are expressed that attracts T_H2 lymphocytes while, the T_H1 attracting chemokines are CXCL10 (IP-10), CXCL9 (Mig-1), CCL2 (MCP-1), CCL3 (MIP-1α), CCL5 (RANTES), and CXCL1 (GROα).[100] Many cancers secrete CCL21, a known chemoattractant for various leukocytes and lymphoid tissue inducer cells, which drive lymphoid neogenesis. In addition, chemokines-CCL2 and CCL5- have long been associated with the recruitment of TAM in tumors,[113] and CXCL5 and CXCL12 can employ MDSCs that alike TAMs, are important effectors in tumor angiogenesis, as discussed in the earlier section.[110]

High plasma concentrations of inflammatory cytokines-IL-6, IL-8, IL-1, TNF-α, and IFN-γ, have been reported with tumor promoting activities. IL-6 protects normal and premalignant intestinal epithelial cells from apoptosis and promotes the proliferation of tumor-initiating cells. It is also involved in macrophage-mediated wound healing, but thus far the evidence of its angiogenic activity is still lacking. Several in vitro studies reported that it had no effect or even growth-inhibitory effect on endothelial cells. However during embryonic development of mice, IL-6 expression was noted to transiently coincide with the early onset of vascular formation, suggesting that this interleukin could play some role in vasculogenesis.[102] TNF-α, another major cytokine, is involved in macrophage- associated angiogenesis. IL-1 is required for tumor invasiveness and angiogenesis[105] and along with TNF-α and IL-6, it has also been known to augment the capacity of cancer cells to metastasize by affecting multiple steps of the Cancer-Related Inflammation (CRI) cascade. The additive effect of many other cytokines has also been reviewed: TNF-α, IL-6, and IL-10 promotes tumor growth, and IL-17, TNF-α, and TGF-β together supports angiogenesis. Other cytokines, IL-8 is mitogenic to endothelial cells and stimulates angiogenesis in animals and TGF-β promotes invasion. TLR9 agonists may promote IL-8 and TGF-β1 production in human prostate cancer cells through NF-kB activation.[114] IFN-γ is involved in antigen representation by macrophages and dendritic cells to T cells[100] (Table 1).

NF-kB and STAT signaling ensure a constant supply of chemokines as well as other cytokines for tumor's angiogenic, invasive, or metastatic behavior in epithelial to mesenchymal transition.[115,116] TLR (Toll-like Receptor) signaling is yet another known mode to enhance tumor development. In a mouse model with transplanted metastatic multiple myelomas, ligands for TLR7 and 9 were shown to stimulate antiapoptotic cancerous growth.[116] STAT3 also regulates the balance between IL-12 and IL-23 in the tumor micro-environment and consequently, affects the polarization of T_H subsets.

5 | IMMUNOTHERAPY AND CANCER

During the late 18th century, immunotherapy was introduced by William Coley as "Coleys Toxin," however,

TABLE 1 Role of chemokines and cytokines in tumor micro-environment

S. No.	Name of chemokines and receptor	Action	References
1	CXCR3, CXCL9, CXCL10, and CXCL11	Induce anti-tumor activities	131
2	CCR5	Anti-metastatic	132
3	CXCL14	Progression and metastasis in breast cancer, lung cancer	133
4	CXCR4/CXCL12	Progression and metastasis, kidney cancer, breast cancer,	103,134–136
5	CCR9/CCL25	Cutaneous melanoma, breast cancer, prostate cancer, Lung cancer	109,137–140,136–139
6	(CXCL13/CXCR-5)	Breast cancer, neuroblastoma, prostate, colon cancer	140–143
7	CXCR4, CCR7, and CCR9	cutaneous melanoma	144
8	CX3CR1/CX3CL1	Prostate cancer	145
9	CXCR6/CXCL16	Lung cancer, hepatocellular cancer	146–149
10	CXCL13	Non-Hodgkin's lymphoma	150
11	CCL17, CCL11, CCL22	Hodgkin's lymphoma	151
12	CXCL10, CXCL9, CCL2, CCL3, CCL5, CXCL1	Hodgkin's lymphoma	151
13	TNF-α, IL-17	Ovarian cancer	152
14	IL-1	Gastric cancer	153
15	TNF-α, IL-10, IL-6	Cervical cancer, prostate cancer	154
16	IL-1β, TNF-α, and TGF-β	Ovarian epithelial cancer	155

due to fewer evidence of efficacy as well as a well-established mechanism it could not become a breakthrough study. Thereafter monoclonal antibodies, as cell check point blockade, proved as milestones in therapy for example, ipilimumab potentially targets the CTLA4 (inhibitor of cytotoxic T cells). Although the clinical trials were not very satisfactory but its mechanism drew the attention of many researchers.[117] Similarly, Nivolumab- checkpoint inhibitors of PD-1 (a negative regulator of T cells) had a significant antitumor activity. Recently, Food and Drug Administration approved a combined effect of ipilimumab and Nivolumab which showed very high response rate and remarkably decreased the level up to 58% against advanced BRAF (gene that encodes a protein B-Raf) wild-type melanoma.

The aim of cancer vaccines is to induce tumor-specific effector T cells that can reduce the tumor mass specifically and that can induce immunological memory to control tumor relapse.[118] Dendritic cells ex vivo generated DC vaccine; Sipuleucel-T is only cellular approved vaccine effective against prostate cancer. Many cytokines such as IFN-γ and IL-9, IL-2 inhibit tumor growth by inhibiting cellular proliferation, neo-angiogenesis, and activate early T cells.[119–121] Similarly, ex vivo generated Epstein Barr virus (EBV) specific and cytomegalovirus (CMV) specific CTLs have been used for the successful treatment of many carcinoma.[122]

Adoptive cell therapy (ACT) which T cells are transferred to a patient can also entirely eliminate the advanced acute lymphoblastic leukemia (ALL) with clinical experimentation in early stage. After collection, the T cells are genetically engineered to produce special receptors on their surface called chimeric antigen receptors (CARs). CARs are proteins that allow the T cells to recognize a specific protein (antigen) on tumor cells. The CART cells are engineered with cyclophosphamide and fludarabine and are then grown in the laboratory in presence of cytokine IL-2 but the major drawback of this technique is post-operative morbidity and invasive nature of the effector molecules.[123] Since the procedure is too harsh to tolerate, adverse side-effects of the treatment have been observed in the patients.[124] Replacing higher concentration of IL-2 with an attenuated one was comparatively tolerable for the patients and has completed the phase I/II trials.[125]

6 | FUTURE PROSPECTIVE

A broad understanding of innate and adaptive immune cells and their secreting molecules will make immunotherapy as an effective and most promising tool in cancer treatment. The adverse effects of chemotherapy, radiotherapy have forced the researchers to develop some alternate strategies as immunotherapy which is specifically based on cellular immunity, antigen-antibody interaction, or chemokines. In

past few years, T, NK, NKT adoptive cells transfer have shown great influence and future perspectives to enhance the efficacy in treatment. But how these cells breakdown the immunosuppressive potential of tumor micro-environment is not fully elucidated. Neoantigens or neo-epitopes of DNA specific alterations or mutation origin also contributes in treatments.[126] The molecular identification of human cancer-specific antigens has led to the development of antigen-specific immunotherapy and immune checkpoint inhibitors.[116,118] Another novel approach is through targeting the CEACAM1/TIM-3 interaction as a T_{reg} exhaustion mechanism in immuno-oncotherapy.[127]

The future antitumor era will be based on different combinatorial trials and synergistic action of drugs. Despite the success rate of combinatorial drugs, they are not permitted for clinical use due to lack of mechanism driven biomarkers.[128,129] On the other hand, some cancer types with mismatch repair (MMR) deficiency like, colon cancer are found to be resistant to most of the therapeutics.[130]

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ORCID

Monisha Dhiman http://orcid.org/0000-0001-5923-3384

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