Cancer Immunology: The Immune System's Response to the Presence and Progression of Cancer

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Introduction

Cancer remains a leading cause of morbidity and mortality on a global scale. It accounts for one in eight deaths worldwide.[1] The number of cancer cases was estimated to be 18.1 million in 2018, with projections suggesting an increase to approximately 23.6 million by 2030[2] dan 29.4 million by 2040[3]. Cancer is a genomic disorder, characterised by the accumulation of point mutations and structural genetic alterations as the disease progresses.[4] These alterations eventually enable cancer cells to express cancer antigens, which the immune system recognises as non-self molecules, thereby eliciting an immune response.[5] The interaction between the immune system and cancer cells is complex, spanning the entire course of cancer development, including metastasis. This intricate interaction can both suppress and promote tumour growth, a phenomenon known as 'immunoediting'.[5,6] One of the cancer therapies currently being developed is immunotherapy, which includes adoptive cell transfer (ACT) and immune checkpoint inhibitors (ICIs).[7] However, the efficacy of these therapies remains limited to certain cancer types.[7] Optimising cancer treatment, particularly immunotherapy, requires a profound understanding of the interactions between the immune system and cancer cells. The study of cancer immunology is one of the most significant achievements in the history of medical science. Most research in this field has focused on the mechanisms through which the immune system eliminates cancer cells. However, understanding how cancer cells evade immune surveillance is equally crucial. This mini-review aims to summarise the integration of these two mechanisms, illustrating how the immune system responds to the presence of cancer cells within the host in a concise yet comprehensive manner, and exploring how these interactions influence cancer development and progression.

Tumor dan Imunitas

In the early 1900s, Paul Ehrlich was the first to propose that if immunity could not control cancer, it would become highly prevalent in long-lived organisms. Later, in the 1950s, Macfarlane Burnet introduced the concept of "immune surveillance," suggesting that the physiological function of the immune system is to recognise and destroy transformed cells before they form tumours, and to eliminate tumours if they do form.[8] This hypothesis led to the premise that cancer cells must express antigens [tumour antigens (Table 1)]—products of malignant transformation events—to be recognised by the immune system.

During transformation, mutant genes result in aberrant gene expression, including proteins that may be immunogenic.[8,9] For cancer cells to be eliminated by antitumour agents—such as cytotoxic T lymphocytes (CTLs), natural killer (NK) cells, and antitumour macrophages—they must be sufficiently antigenic.[10] Further discussion on this topic will be presented in the following subsections.

Table 1. Kategori antigen tumor pada manusia[11]

Category	Tumor Antigen (TA)	Cancer Histology
Onkofetal	CEA	Karsinoma kolorektal
	Immature laminin receptor	RCC
	TAG-72	Karsinoma prostat
Onkoviral	HPV E6, E7	Kanker serviks
Over-expressed	BING-4	Melanoma
	Calcium-activated chloride channel 2	Karsinoma paru
	Cyclin-B_1	Multi
	9D7	RCC
	Ep-CAM	Karsinoma payudara
	EphA3	Multi
	Her2/neu	Multi
	Telomerase	Multi
	Mesothelin	Karsinoma duktus pankreas
	SAP-1	Karsinoma kolorektal
	Survivin	Multi
Kanker-Testis	BAGE family	Multi
	CAGE family	Multi
	GAGE family	Multi
	MAGE family	Multi
	SAGE family	Multi
	XAGE family	Multi
	CT9, CT10	Multi
	NY-ESO-1/LAGE-1	Multi
	PRAME	Multi
	SSX-2	Melanoma, Multi
Lineage restricted	Melan-A/MART-1	Melanoma
	GP100/pmel17	Melanoma
	TRP-1/2	Melanoma
	P-polypeptide	Melanoma
	Tyrosinase	Melanoma
	MC1R	Melanoma
	Prostate-specific antigen	Prostat
Mutated	Β-catenin	Melanoma, Prostat, HCC
	BRCA1/2	Karsinoma payudara, ovarium
	CDK4	Multi
	CML66	CML
	Fibronectin	Multi
	MART-2	Melanoma
	p53	Multi
	Ras	Multi
	TGF-β RII	Karsinoma kolorektal
Posttranslationally altered	MUC1	Karsinoma duktus, RCC
Idiotypic	Ig, TCR	Leukemia B,T, limfoma, mieloma

Sel natural killer (NK)

Natural killer (NK) cells are a component of the innate immune system, with a relatively shorter half-life compared to B and T cells. The cytotoxic capabilities of NK cells allow them to eliminate tumour cells, even when present in relatively small numbers. NK cells play a crucial role in clearing virus-infected cells or cells that have undergone oncogenic transformation. Several in vivo studies have demonstrated that NK cells limit the metastatic spread of melanoma. NK cells have also been reported to initiate antitumour T-cell responses by recruiting type I conventional dendritic cells (cDC1) through chemokine signalling (via XCL-1 and CCL5/RANTES),[12] and by supporting dendritic cell stimulation through the expression of Flt3 ligands (Flt3l in mice and FLT3LG in humans).[13] Research has shown that the number, infiltration, and function of NK cells correlate with increased patient survival rates.[14] An illustration of the interaction between NK cells and tumour cells is provided in Figure 1. Mature human NK cells express various stimulatory and inhibitory receptors encoded by the germline. These receptors bind specific ligands that are either constitutively expressed or induced on tumour cells during transformation. The level of tumour ligand expression and NK cell receptor engagement (as shown in Figure 1) determines whether NK cells will kill the tumour cells or not. NK cells also express receptors for activating cytokines [such as interleukin-10 (IL-10), IL-21, IL-18, and IL-12] as well as inhibitory factors [such as transforming growth factor-β (TGF-β) and activin-A]. The balance between soluble activating and inhibitory factors further influences the integration of NK cell receptor signalling. Thus, the sum (Σ) of these signalling inputs regulates NK cell activation and tumour cell lysis.

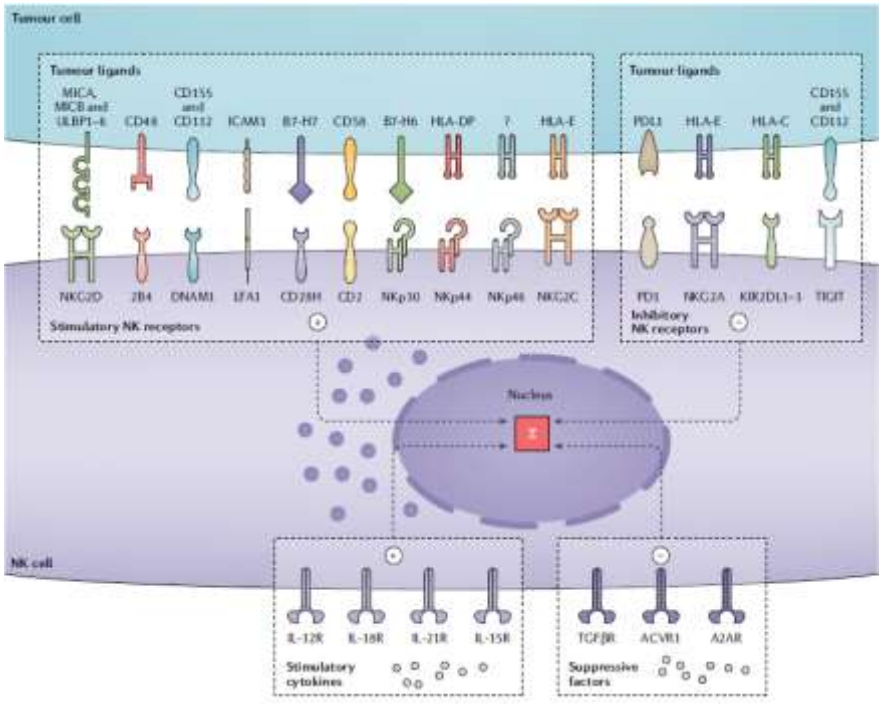


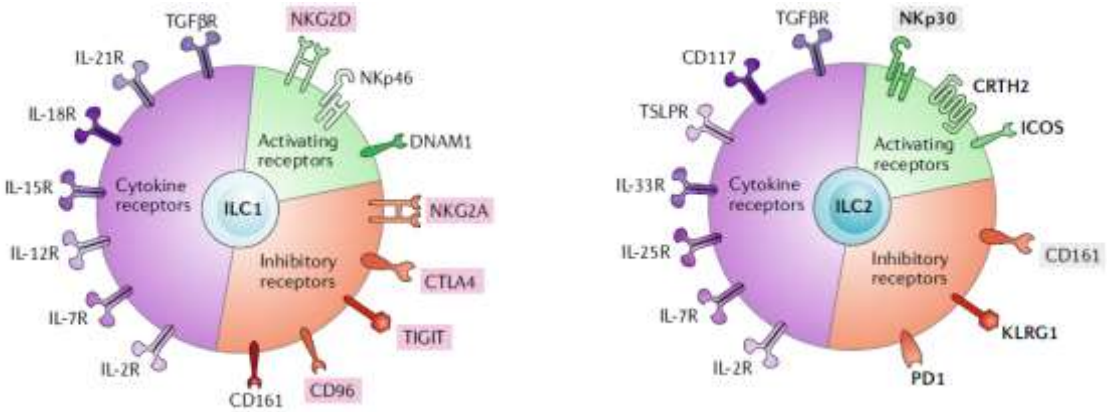
Figure 1. Tumour and NK cells interaction.[15]

Non-NK Cell Innate lymphoid cells (ILCs)

The role of non-NK ILCs (Innate Lymphoid Cells) is not well understood and seems to vary significantly depending on the cytokine composition in the tumour microenvironment. ILC2s are capable of influencing adaptive immune responses through the expression of MHC Class II molecules on their surface and by promoting antigen-specific CD4+ T cell responses.[16] Furthermore, the secretion of IL-13 by ILC2s is known to be important in the migration of activated dendritic cells to tumour-draining lymph nodes, where these dendritic cells play a role in promoting cytotoxic T cell responses.[17] Conversely, the MHC Class II molecules expressed by ILC3s tend to have a regulatory function in the expansion of the CD4+ T cell population, although the precise role of ILC3s in cancer remains unclear.[18] Figure 2 will provide an illustration of several key receptors involved in antitumour events in ILCs.

Makrofag

Macrophages constitute 50% of the total immune cells infiltrating the tumour stroma.[19] Macrophages exhibit high plasticity, and depending on their induction, they can polarise into M1 and M2 phenotypes. M1 macrophages tend to be pro-inflammatory, making them more effective in eliminating cancer cells. In contrast, M2 macrophages are typically anti-inflammatory, allowing them to create an immunosuppressive environment around cancer cells.[20] M1 macrophages express a range of MHC Class II molecules to initiate antitumour immune responses.[21] M1 macrophages are known to enhance direct killing events[22] and act as inhibitors of metastasis and cancer growth.[23] An increase in the number of M1 macrophages in the tumour microenvironment is a predictor of patient survival.[23] M2 macrophages tend to perform phagocytic functions.[28] M2 macrophages are also known to play a pro-tumour role and are generally a representation of tumour-associated macrophages (TAMs). The pro-tumour effects of M2 macrophages stem from their ability to promote genetic instability, local immunosuppression, and the maintenance of stem cells.



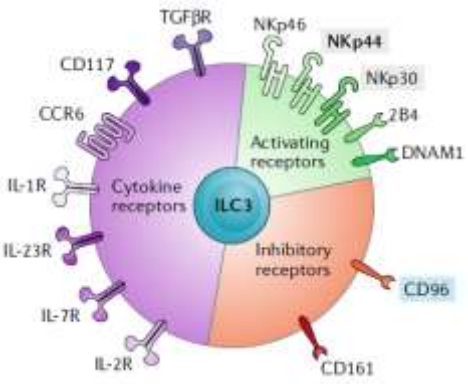


Figure 2. Surface receptors expressed by human and mice ILCs.[15] The figure shows the activating (green), inhibitory (red), and cytokine (purple) receptors expressed on the surface of ILCs in mice and humans. The grey blocks indicate receptors that are only found in humans, the blue blocks indicate that there is no evidence supporting the expression of these receptors by ILCs in mice, and the pink blocks indicate that there is no evidence supporting the expression of these receptors by ILCs in humans. Non-cytokine receptors expressed by the ILC1, ILC2, and ILC3 families are classified as either activating or inhibitory receptors based on their structural characteristics and their effects on NK cells and/or T cells. However, there are exceptions, as some receptors, marked in bold, have demonstrated functions in ILC2 and ILC3. ILC2 express the inhibitory receptors lectin-like receptor subfamily G member 1 (KLRG1) and programmed cell death protein 1 (PD1), which are involved in regulating ILC2 population expansion and cytokine secretion.[24] ILC2 also express CRTH2 and natural killer cell p30-related protein (NKp30), and activation of these receptors induces cytokine production and, in the case of CRTH2, cell migration.[25] Both mouse and human ILC2 express inducible T cell costimulator (ICOS), which promotes their survival and cytokine production.[26] Cytokine production is induced by the binding of NKp44 on ILC3, defining this receptor as an activating receptor, similar to NK cells.[27] CCR6, CC-chemokine receptor 6; CTLA4, cytotoxic T lymphocyte antigen 4; DNAM1, DNAX accessory molecule 1; IL-33R, IL-33 receptor (also known as IL1RL1); KIR, killer cell immunoglobulin-like receptor; LAG3, lymphocyte activation gene 3 protein; TIGIT, T cell immunoreceptor with Ig and ITIM domains; TIM3, T cell immunoglobulin mucin receptor 3; TSLPR, thymic stromal lymphopoietin protein receptor.

The Relationship Between Tumour Formation and Immune Response

The question of how and who plays a role in the development and defence of cancer cells cannot be separated from the cancer cells themselves, normal stromal cells, and host immunity. Other factors such as cellular changes due to infections or stress triggered by diseases may also contribute to tumour growth or suppression. $CD8^+$ cytotoxic T cells and $CD4^+$ Th1 (helper) T cells generally inhibit cancer development through a mechanism involving interferon (IFN)-γ and cytotoxins,[29] while, on the other hand, chronic inflammation (Table 2) can control these antitumour effects and promote cancer development.[30,31] Several studies have shown that both the development of colon and pancreatic tumours in mouse models and human colon and pancreatic cancers are driven by chronic inflammation. From Table 2, we can also see that autoimmune diseases support the development of many cancers, including lymphoma, as shown in recent experiments.

Table 2. The association between induced-inflammatory agent with some cancer.[31]

Malignancy	Inflammation Stimuly
Bladder	Schistosomiasis
Cervical	Papillomavirus
Ovarian	Pelvic inflammatory disease/talc/tissue remodeling
Gastric	H pylori induced gastritis
MALT lymphoma	H pylori
Oesophageal	Barrett's metaplasia
Colorectal	Inflammatory bowel disease
Hepatocellular	Hepatitis virus (B and C)
Bronchial	Silica, asbestos, cigarette smoke
Mesothelioma	Asbestos
Kaposi's sarcoma	Human herpesvirus type 8

Tumour Progression and Immunity

Significant discoveries have been made over the past few decades, shedding light on the mechanisms of "immunoediting" (Figure 3), which reveals that the immune system can both inhibit and promote tumour cell development.[6] The immune system typically recognises tumour cells that highly express tumour antigens, as illustrated in Table 1. In other words, the immune system can eliminate tumour cells that are vulnerable to immunity or are immunogenic.[32] However, an equilibrium state can also occur, wherein the growth of tumour cells due to genetic instability coincides with their elimination by the immune system. This 'equilibrium' state may induce tumour dormancy.[33] Unfortunately, this equilibrium can eventually lead to 'tumour escape,' where tumour cells evade immunity by suppressing immune function or by downregulating the expression of tumour antigens targeted by the immune system.[34]

The mechanisms through which the immune system kills tumour cells during the elimination phase are depicted in Figure 4. Innate immune components such as NKT cells, NK cells, and $\gamma\delta$ T cells recognise the accumulation of transformed cells and subsequently produce IFN-γ. This cytokine triggers a cascade of innate immune reactions, involving:

(1) Induction of angiostatic chemokines (CXCL10 (IP10), CXCL9 (MIG), and CXCL11 (I-TAC)) that inhibit tumour neovascularisation and recruit effector immune cells like NK cells, dendritic cells, macrophages, and others to the site of recognition.
(2) Antiproliferative effects of IFN-γ on developing tumour cells
(3) Activation of cytocidal activities of macrophages and NK cells infiltrating the tumour cell population.

These events facilitate tumour cell death through both immunological and non-immunological mechanisms. Debris from dead tumour cells is phagocytosed by dendritic cells and transported to draining lymph nodes to aid in the development of tumour-specific CD4+ and CD8+ T cells. Concurrently, macrophages and NK cells continuously

monitor tumour cell growth within the population. Once the maturation of $CD4^+$ and $CD8^+$ T cells is complete, these adaptive immune cells are guided by chemokine gradients to the site of tumour recognition.

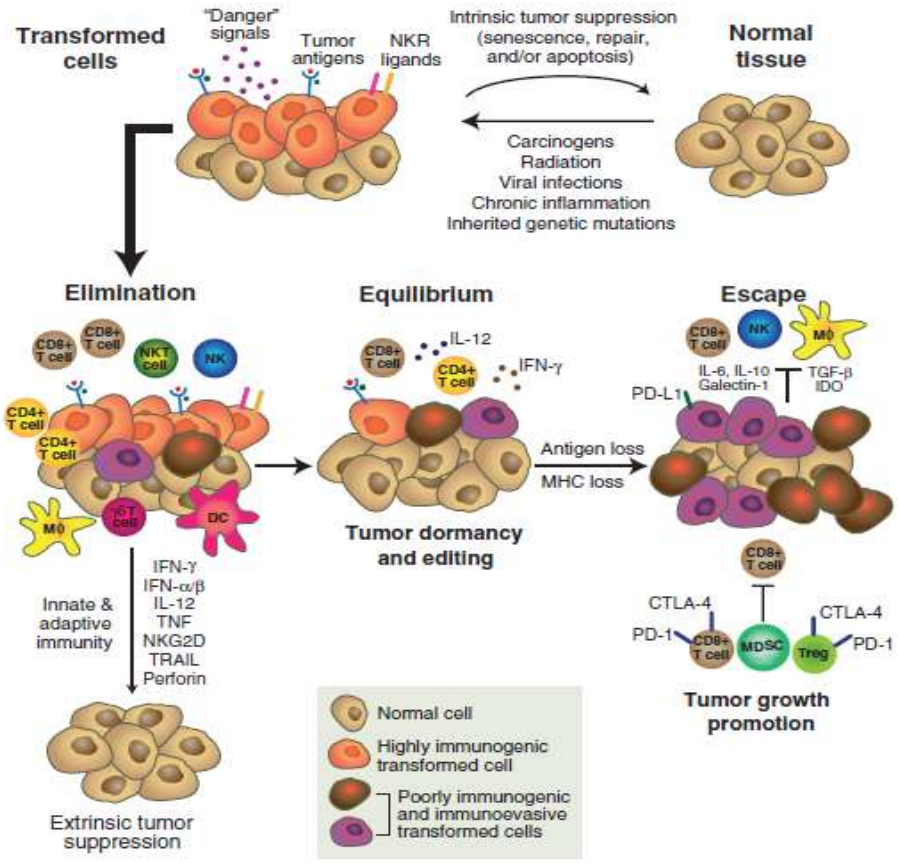


Figure 3. The Concept of Cancer Immunoediting. Cancer immunoediting is an extrinsic tumour–suppressing mechanism that operates only after cellular transformation has occurred and intrinsic tumour–suppressing mechanisms have failed. The most complex form of immunoediting comprises three stages: elimination, equilibrium, and escape (the three Es).[5] **(a) Elimination**: In this phase, the innate and adaptive immune systems collaborate to recognise and eliminate tumour cells (immunosurveillance) before the tumour becomes clinically detectable. The success of the elimination phase determines the likelihood of the host remaining tumour–free. **(b) Equilibrium**: In this phase, the immune system eliminates tumour cells while simultaneously promoting the emergence of new tumour cell variants. These variants generally have the capacity to evade immune attacks, eventually leading to the escape phase. T cells, IL–12, and IFN–γ are essential to maintaining tumour cells in a state of functional dormancy. In contrast, NK cells or other molecules involved in innate immunity are not required during the equilibrium phase, indicating that equilibrium is highly dependent on adaptive immune function. Continuous selection by the immune system of genetically unstable tumour cells can lead to the emergence of new tumour cell variants with resistance to immune surveillance. These new tumour variants escape immune control and enter the escape phase. **(c) Escape**: In this phase, the majority of tumour cells evade immune surveillance, resulting in the uncontrolled growth of tumour cell variants. In diagram (a) and (b), blue cells represent developing tumour cells, red cells represent tumour cell variants, and grey cells represent stromal and normal cells that have not yet undergone transformation. In diagram (c), additional tumour cell variants are depicted as orange cells. The diagram also illustrates various lymphocytes, marked accordingly, with small orange circles representing cytokines.[35]

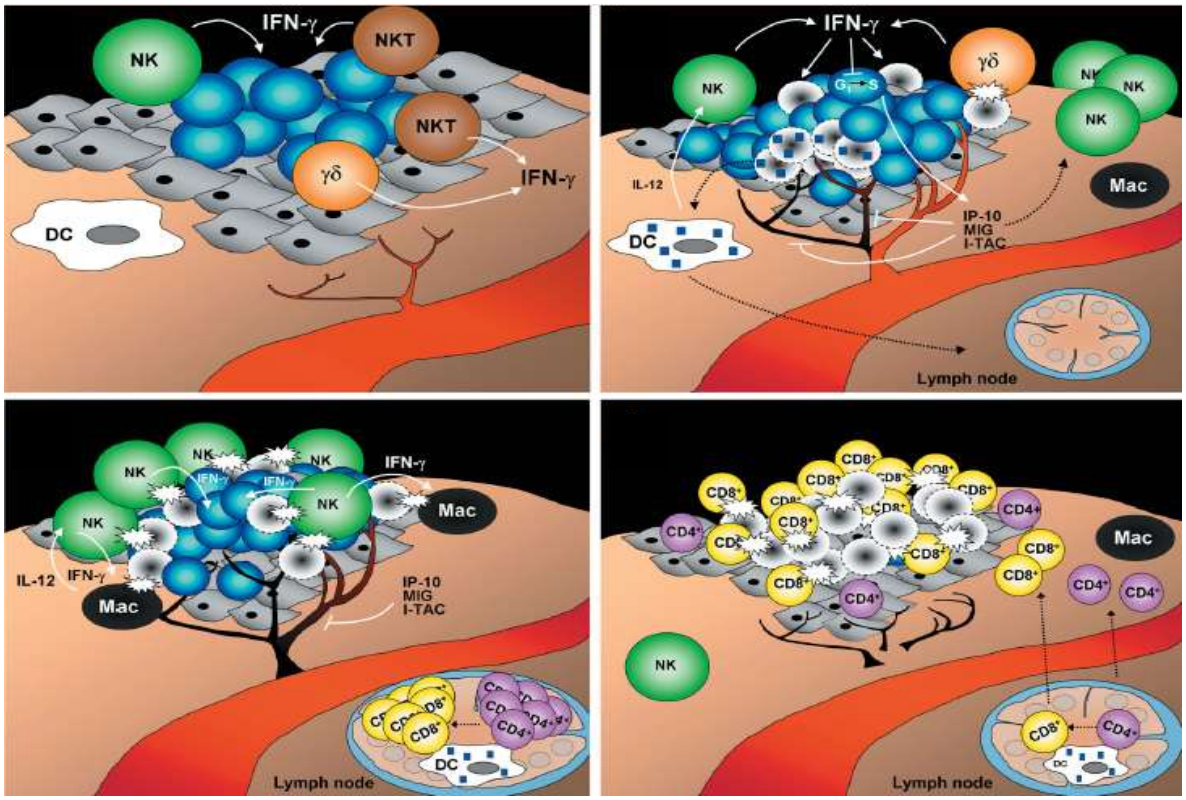


Figure 4. A proposed model of elimination during cancer immunoediting events, as suggested by several experts.[35] Tumour cells are represented in blue, non-transformed cells are represented in grey, tumour cell debris is shown as a white-to-grey gradient enclosed within dashed lines, and the lymphocyte cells involved are labelled accordingly in the diagram.

Factors Used by Tumour Cells to Evade the Immune System

Regulatory Cells

Immunosuppression in the tumour microenvironment (TME) is mediated by $CD4^+CD25^+FoxP3^+$ Tregs and other suppressive cells.[36] This leads to tumour escape and poses significant challenges for cancer immunotherapy development. Research has shown that tumour-derived Tregs exhibit stronger suppressive activity than naturally occurring Tregs.[37] Tregs are attracted to the TME by chemokines. Certain studies also indicate that TGF-β produced by tumour cells facilitates the conversion of $CD4^+$ T cells into suppressive Tregs in situ.[38] Thus, eliminating Tregs using anti-CD25 monoclonal antibodies (mAbs) or other methods can enhance tumour rejection. Myeloid-derived suppressor cells (MDSCs) modulate dendritic cells and alternatively activate M1 and M2 macrophages, fostering an inflammatory microenvironment that promotes tumour initiation, angiogenesis, and metastasis. Some experts argue that a "vicious cycle" arises from elevated inflammatory mediators, enabling MDSC resistance to apoptosis and ultimately causing T-cell downregulation.[39] Reducing chronic inflammatory mediators through pharmacological agents may decrease MDSC numbers and mitigate immunosuppression. Thus, $CD11b^+Gr1^+$ MDSCs suppress antitumour immunity mediated by T cells, a mechanism potentially involving the downregulation of the TCR-ζ chain.

Consequently, reducing chronic inflammatory mediators through pharmacological agents is considered to decrease MDSC numbers and alleviate immunosuppression.[40] On the other hand, $CD11b^{+}F4/80^{+}$ macrophages with an M2 phenotype produce high levels of TGF-β, IL-10, and vascular endothelial growth factor (VEGF), thereby promoting tumour growth. Additionally, several tumour-derived factors and gangliosides have been reported to alter dendritic cell (DC) phenotypes. Functionally impaired immature DCs exhibit low levels of CD80, CD86, and CD40 but express high levels of indoleamine 2,3-dioxygenase (IDO), which also contribute to T-cell immunosuppression.

Tabel 3. The Population of T-cell Regulatory.[38]

Cell Subset	Predicted Origin	Experiment Design	Suppresive Mechanism
Subset Sel T CD4+			
Sel T_{reg} $CD4^{+}CD25^{+}FOXP3^{+}$*	Thymus	Autoimmune mice	*In vitro*: cell to cell contact *In vivo*: multiple model action
Sel T_R1 $CD4^{+}IL-10^{+}FOXP3^{-}$*	Perifer	Mice cell culture *in-vitro* with IL-10	IL-10
Sel T_H3 $CD4^{+}TGF\beta^{+}$*	Perifer	Oral-induced tolerant mice	TGF-β
Subset Sel T CD8+			
Sel T $CD8^{+}CD25^{+}$	Thymus	Human thymus	TGF-β and CTLA4
Sel T $CD8^{+}CD28^{-}$	Perifer	Allgenic transplant organ in human	Targetting ILT3 and ILT4 on the dendritic cells
Sel T $CD8^{+}CD62L^{+}CD122^{+}$	ND	Normal neonatal mice	ND
Sel T $CD8^{+}IL-10^{+}$	Perifer	Human ovary cancer cell culture *in-vitro*	IL-10

*$CD4^{+}$ regulatory T cells are conceptually divided into three populations. **$CD4^{+}CD25^{+}FOXP3^{+}$ T cells**: These are thought to originate from the thymus and are referred to as naturally occurring regulatory T cells (Treg cells). **$CD4^{+}IL^{-}10^{+}FOXP3^{-}$ T cells**: These can be induced *in vitro* through various protocols or *in vivo* in response to challenges from exogenous antigens. These are referred to as adaptive regulatory T cells or regulatory T 1 cells (TR1 cells). **$CD4^{+}TGF\beta^{+}$ T cells**: These are induced in the context of oral tolerance and are referred to as TH3 cells. Importantly, within this classification, cytokine patterns and suppressive mechanisms are not mutually exclusive and often overlap. For instance, tumour-associated CD4+CD25+ Treg cells in humans and mice express both IL-10 and FOXP3. **Abbreviations**: **CTLA4** → Cytotoxic T-lymphocyte-associated antigen 4; **FOXP3** → Forkhead box P3; **ILT** → Immunoglobulin-like transcript; **ND** → Not determined; and **TH** → T helper.

Impaired Antigen Presentation

Another mechanism that allows tumours to evade immunity involves weakening the antigen processing machinery, such as MHC class I molecules, proteasome subunits (LMP-2, LMP-7), transporter associated with antigen processing (TAP), and tapasin. This downregulation of tumour antigens results in the inability of cytotoxic T cells (CTLs) to recognise tumour antigens, enabling tumour cells to grow and proliferate.[41,42]

Immunity Suppressing Mediator

Tumours also suppress immune responses through immunosuppressive cytokines expressed by both tumour and non-tumour cells in the TME. Key immunosuppressive mediators include TGF-β, TNF-α, IL-1, IL-6, CSF-1, IL-8, IL-10, and type I IFN, all of

which significantly contribute to tumour growth. VEGF inhibits dendritic cell differentiation, reducing antigen presentation efficiency. IL-10 and TGF-β also hinder dendritic cell maturation, leading to tolerogenic immature DCs that cannot effectively present antigens to T cells. Tumour-associated antigens such as gangliosides and RCAS1 further suppress CTL and dendritic cell functions or induce apoptosis in tumour-infiltrating lymphocytes (TILs). Immunosuppressive enzymes such as IDO, arginase, and IKK-2 either directly facilitate tumour proliferation or indirectly induce T-cell suppression or tolerance.

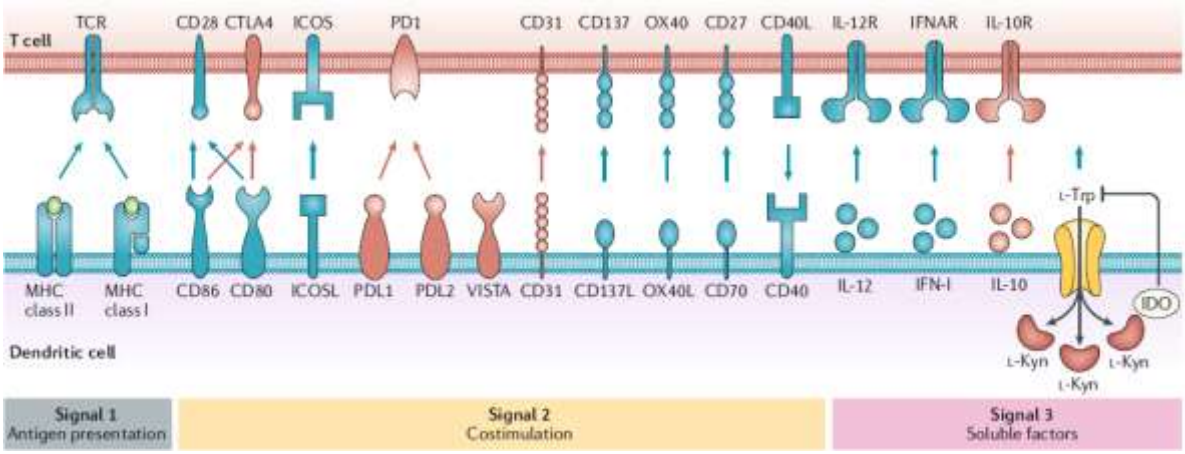


Figure 5. Illustration of T cell immunity or tolerance induction by dendritic cells.[43] To control T cell activity, dendritic cells express class I and class II MHC molecules. However, the expression of these molecules alone is deemed insufficient to trigger effective antitumor immunity. Therefore, costimulatory molecules (including the B7 protein family and tumor necrosis factor [TNF]) and soluble factors such as IL-12 and type I interferon (IFN-1) are required to initiate positive signaling (blue arrows and their receptors). Conversely, inhibitory mechanisms (red arrows and their receptors) limit T cell activation. ICOS: Inducible T cell costimulator.

Tolerance and Immune Deviation

Under antitumour immune pressure, cancer cell variants that exploit dendritic cells to induce immune tolerance may emerge, as previously discussed in the context of immunoediting. The presentation of tumour-associated antigens (TAA) without accompanying costimulatory signals can induce T-cell anergy. Similarly, the involvement of inhibitory receptors can limit T-cell activity, as shown in Figure 5. CTLA4, expressed on T cells, binds to CD80 and CD86 on dendritic cells with greater affinity than CD28. This interaction limits costimulatory signalling and T-cell activation. Programmed cell death ligands 1 (PDL1) and 2 (PDL2) on dendritic cells and other cells within the tumour microenvironment also inhibit the proliferation and cytokine production of activated T cells that express programmed cell death 1 (PD1). The V-domain immunoglobulin suppressor of T-cell activation (VISTA), another inducible member of the PD1 family expressed on dendritic cells, can also limit T-cell antitumour immunity. CD31, a trans-homophilic inhibitory molecule, can induce a tolerogenic phenotype in dendritic cells, directing T cells to differentiate into Tregs instead of TH1 cells. Dendritic cells also

modulate T-cell function by altering the availability of metabolic substrates, such as L-tryptophan. L-tryptophan, essential for T-cell responses, is entirely converted to L-kynurenine by the enzyme indoleamine 2,3-dioxygenase 1 (IDO1). IDO1 is induced in dendritic cells upon recognition of apoptotic cells and/or binding of CTLA4 to CD80 or CD86. A critical note in this context is that tumour-associated dendritic cells express high levels of IDO1. These dendritic cells have been reported to suppress the proliferation and effector functions of CD8+ T cells, NK cells, and plasma cells, and to contribute to Treg differentiation.

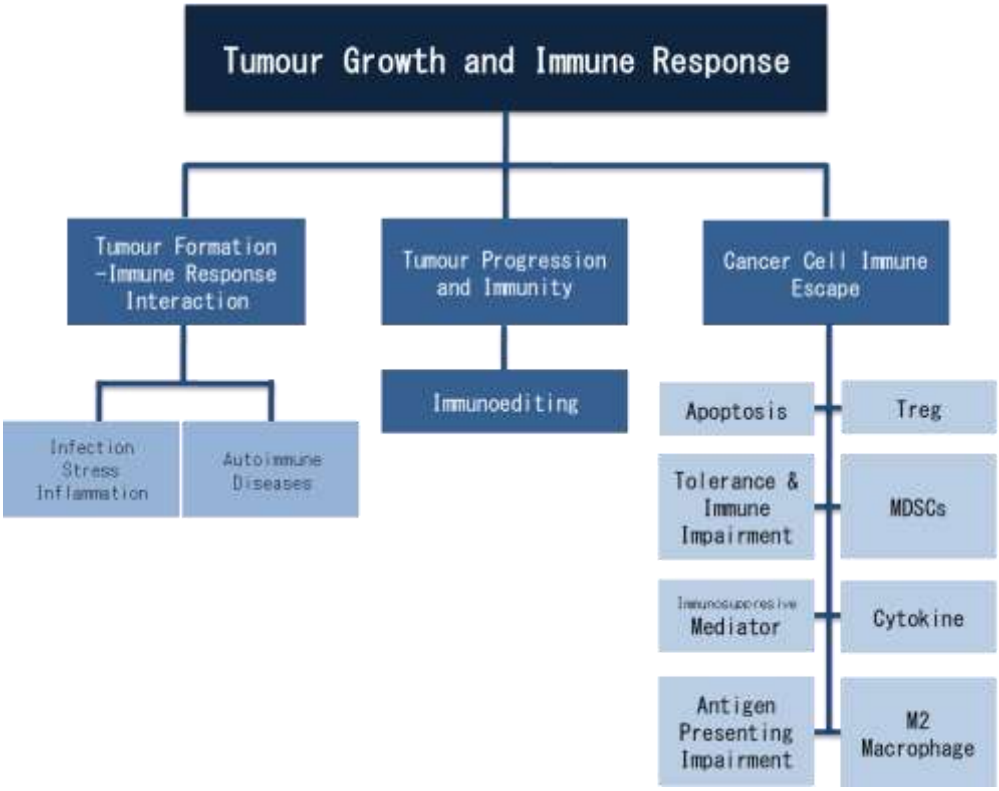


Figure 6. Infographic of tumor growth and immune response (adapted from Vinay et al., 2015[6]). Illustration of key factors regulating tumor formation, progression, and immune evasion. Numbers in parentheses indicate relevant references supporting the statements made.

Apoptosis

Several studies have demonstrated that tumour cells can kill specific cytotoxic T lymphocytes (CTLs). Various factors influencing the mechanisms of tumour growth and immune evasion have been summarised in Figure 6. An illustration of the interactions between cells within the tumour microenvironment that trigger an immunosuppressive state is provided in Figure 7.

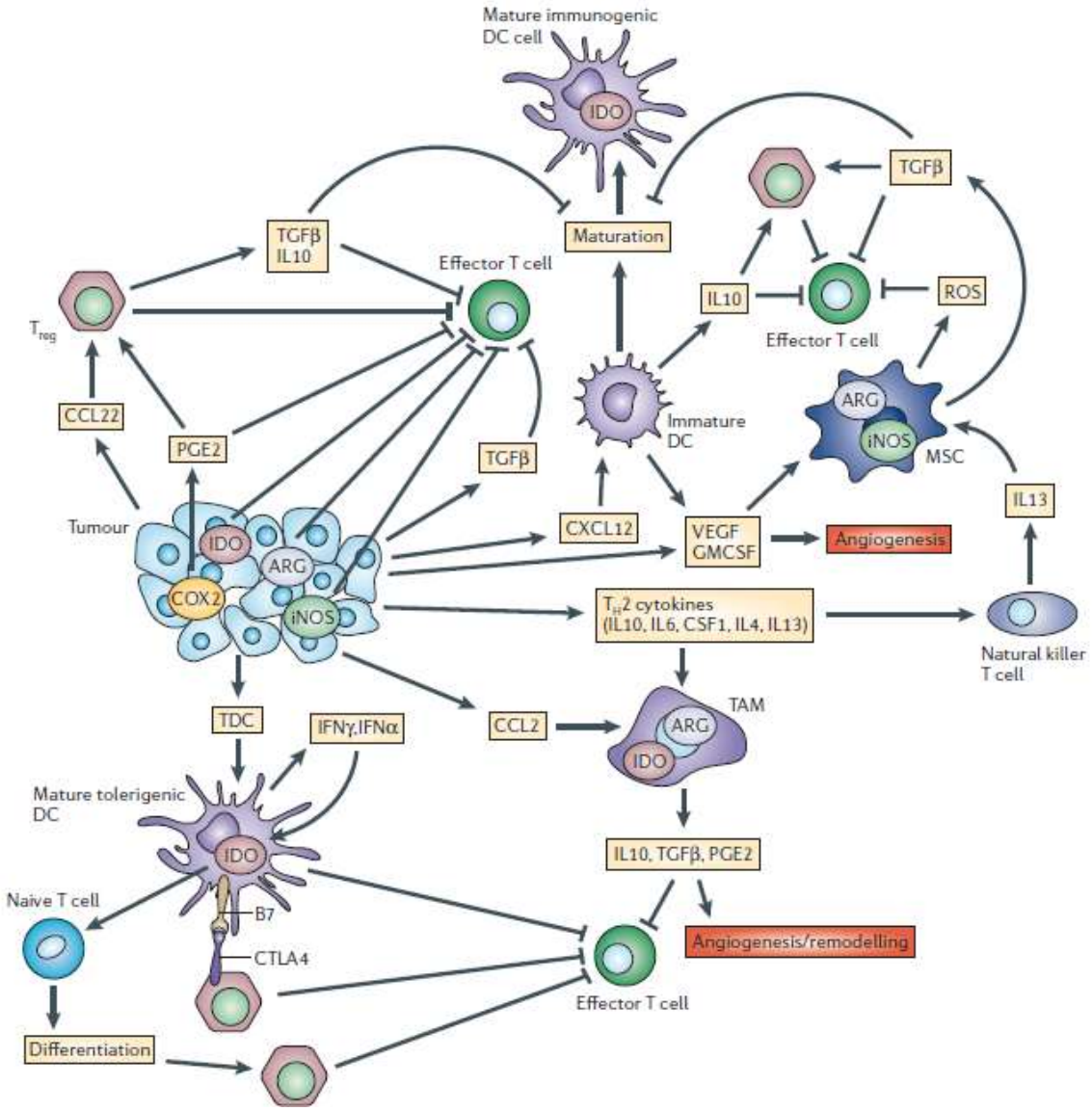


Figure 7. Interaction between tumor cells and the immune system, leading to an immunosuppressive microenvironment.[44] Through the production of cytokines (such as IL-10, TGF-β, IL-13, and vascular endothelial growth factor [VEGF]) and chemokines (such as CCL22, CCL2, and CXCL12), tumors can promote the migration and expansion of cells that regulate the immune system. Regulatory T cells (Tregs) negatively regulate immunity by blocking effector T cells through direct interaction and the production of immunosuppressive cytokines such as TGF-β and IL-10. These cells, along with myeloid suppressor cells (MSCs), immature dendritic cells, natural killer T (NKT) cells, and tumor-associated macrophages (TAMs), can be recruited. These cells act to suppress the proliferation of effector T cells (such as $CD4^+$ helper T cells and $CD8^+$ cytotoxic T cells), cytokine production (such as interferon-γ [IFN-γ] and IL-2), and cytolytic activity. Both tumor cells and host cells can express enzymes involved in immune suppression (such as arginase [ARG], indoleamine 2,3-dioxygenase [IDO], cyclooxygenase 2 [COX2], and inducible nitric oxide synthase [iNOS]). Additionally, mature tolerogenic dendritic cells may accumulate in tumor-draining lymph nodes. IDO activity induced in tolerogenic DCs through interaction with Tregs expressing CTLA4 can further drive Treg expansion and differentiation. Abbreviations: CSF1 → Colony-stimulating factor-1; GM-CSF → Granulocyte-macrophage colony-stimulating factor; PGE2 → Prostaglandin E2; ROS → Reactive oxygen species; TDC → Tumor-derived cytokine.

Sistem metabolisme sel kanker yang cenderung menekan fungsi sel imun

Sejumlah penelitian telah menunjukkan bahwa secara umum transformasi maligna berhubungan erat dengan perubahan metabolisme seluler. Sejumlah perubahan

metabolisme seluler sel–sel kanker dapat memodulasi kinerja sistem imun (Gambar 9), dan menjadikan sistem imun bersifat lebih permisif terhadap aktivitas sel–sel kanker. Pun demikian dengan perubahan keadaan dalam lingkungan mikro tumor yang cenderung menimbulkan kondisi imunosupresif (Gambar 8). Sel–sel imun yang menginfiltrasi dapat mengurangi kadar nutrien di dalam lingkungan mikro tumor, yang secara potensial berkontribusi terhadap lingkungan imunosupresif. Sebagai contohnya, glukosa banyak dimanfaatkan oleh sel dendritik tolerogenik, MDSCs, dan *tumour–adjacent endothelial cells*, yang mana telah diketahui dapat menimbulkan kondisi permisif untuk pertumbuhan tumor dan metastasis. Selain itu, dengan bersaing memperebutkan glukosa, sel T_{reg} dapat menginduksi *replicative senescence* sel T $CD4^+$ dan $CD8^+$.

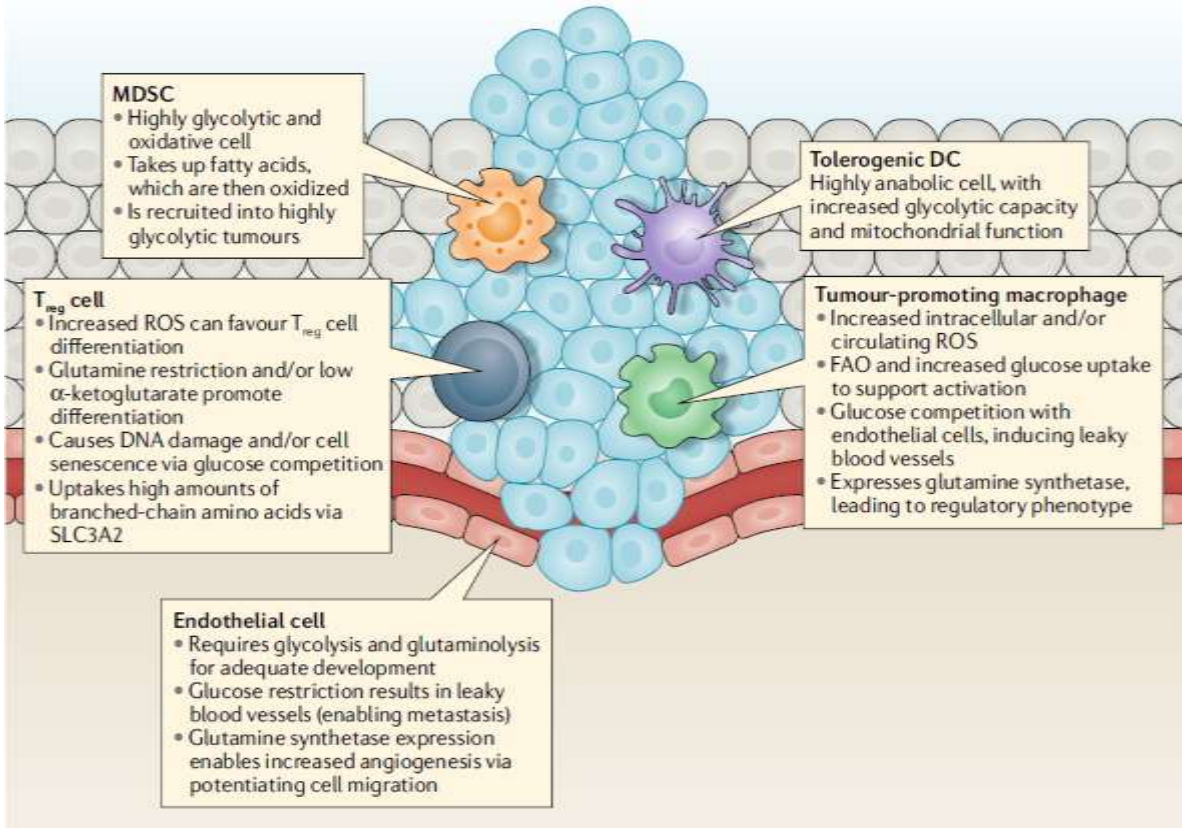


Figure 8. TME supports immune cell metabolism that facilitates tumor growth.[45] Immune cells that facilitate tumor growth are capable of adapting to the tumor microenvironment (TME) and may contribute to nutrient depletion. In this way, these cells contribute to an immunosuppressive environment, enabling tumor growth and immune escape. Abbreviations: FAO → Fatty acid oxidation and ROS → Reactive oxygen species.

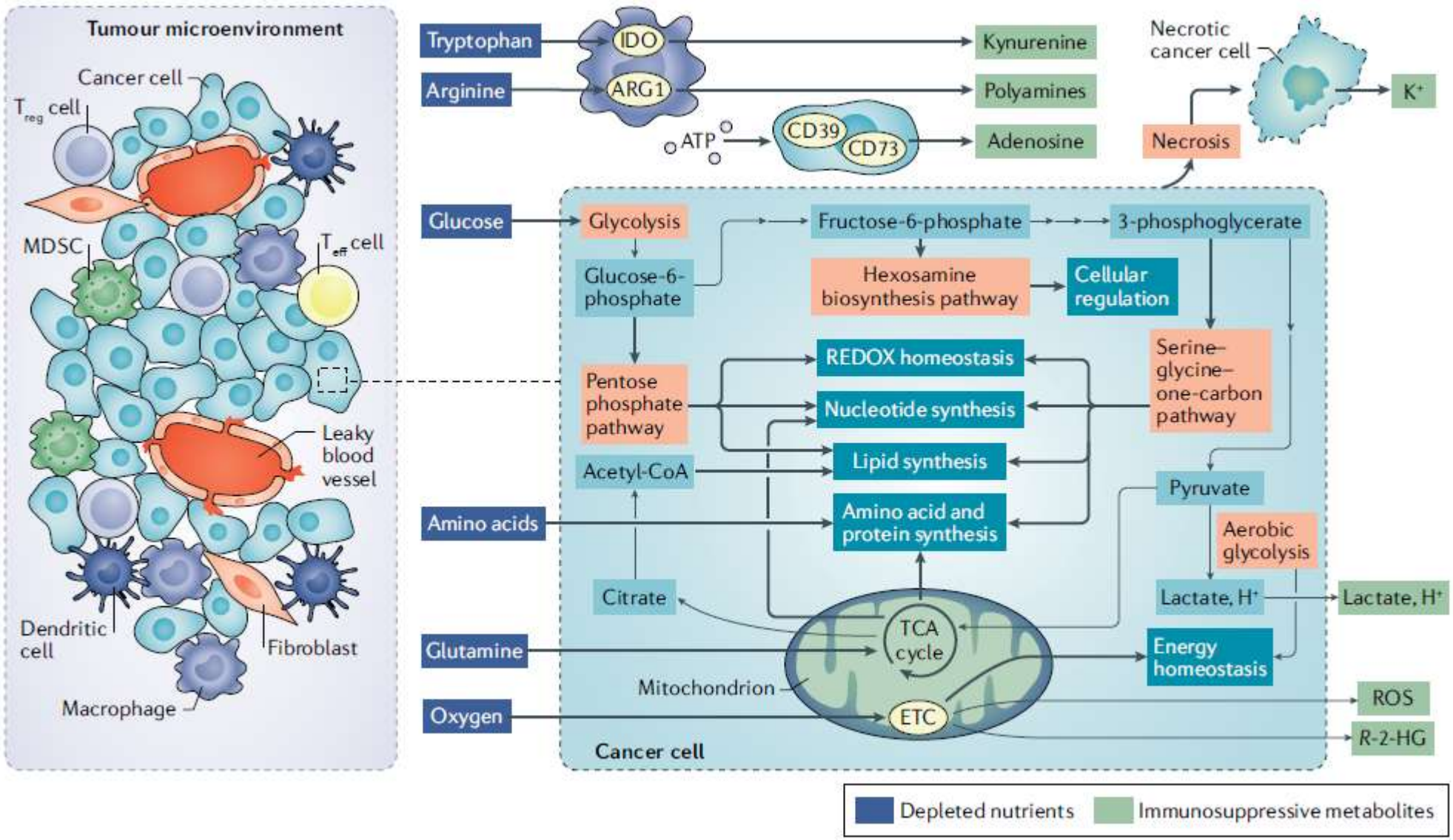


Figure 9. Cancer cell metabolism and metabolic alterations in the tumor microenvironment (TME).[46] The oxidation of nutrients in mitochondria, including glucose, amino acids, and fatty acids, through the tricarboxylic acid (TCA) cycle and the electron transport chain (ETC), is an efficient mechanism for producing energy in quiescent cells. However, during periods of increased proliferation, such as after immune activation or malignant transformation, cells upregulate an alternative pathway for glucose metabolism known as aerobic glycolysis. Although aerobic glycolysis is less efficient in ATP production, it allows faster glucose metabolism, facilitates the removal of excess carbon, and regenerates NAD^+ efficiently while maintaining mitochondrial enzymatic activity for anabolism.

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