Cancer Vaccines

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Disclaimer

I am not an expert in this topic

Not difficult but lots of immunology understanding is necessary

I will try to explain whatever I have read in different literatures and understood

May be boring at times : sorry for that

A whole day is not sufficient to explain this topic

Immune system and Cancer

Innate (nonspecific) defense system

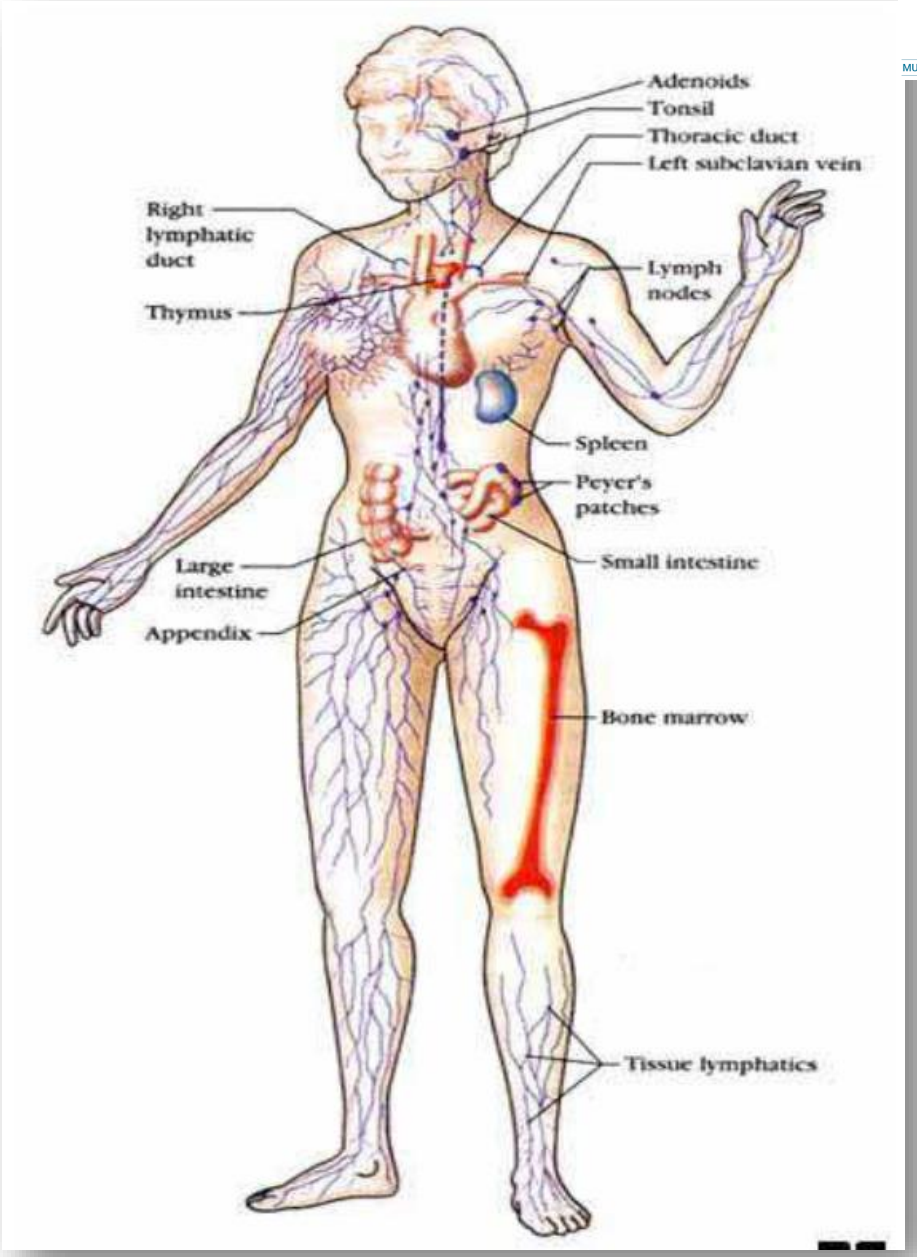
a. surface barriers

b. internal defenses

. Adaptive (specific) defense systems

a. humoral immunity

b. cellular immunity



Innate immunity

- Innate immunity is the immunity that is immediately available without having to adapt to the specific pathogen that is present.
- It is not specific to a particular organism such that identical responses can protect against several organisms.
- Innate immunity is germline encode (evolved on an evolutionary time scale).
- Innate immunity is mediated by phagocytes (cell that ingest bacteria or other particulate matter) such as macrophages and neutrophils.
- It is also mediated by chemical compounds and physical barriers

Adaptive Immunity

- Specific Immune Response (e.g., antibody) against a particular microorganism is an adaptive immune response. That is, it occurs during one's lifetime as an adaptation to the presence of that particular organism. (usually, the term specific means the ability to distinguish one organism from another)

- Specific immunity can be induced by a variety of substances. Things that are targets of adaptive immunity are called **ANTIGENS***

- Antigen-specific responses are mediated by lymphocytes

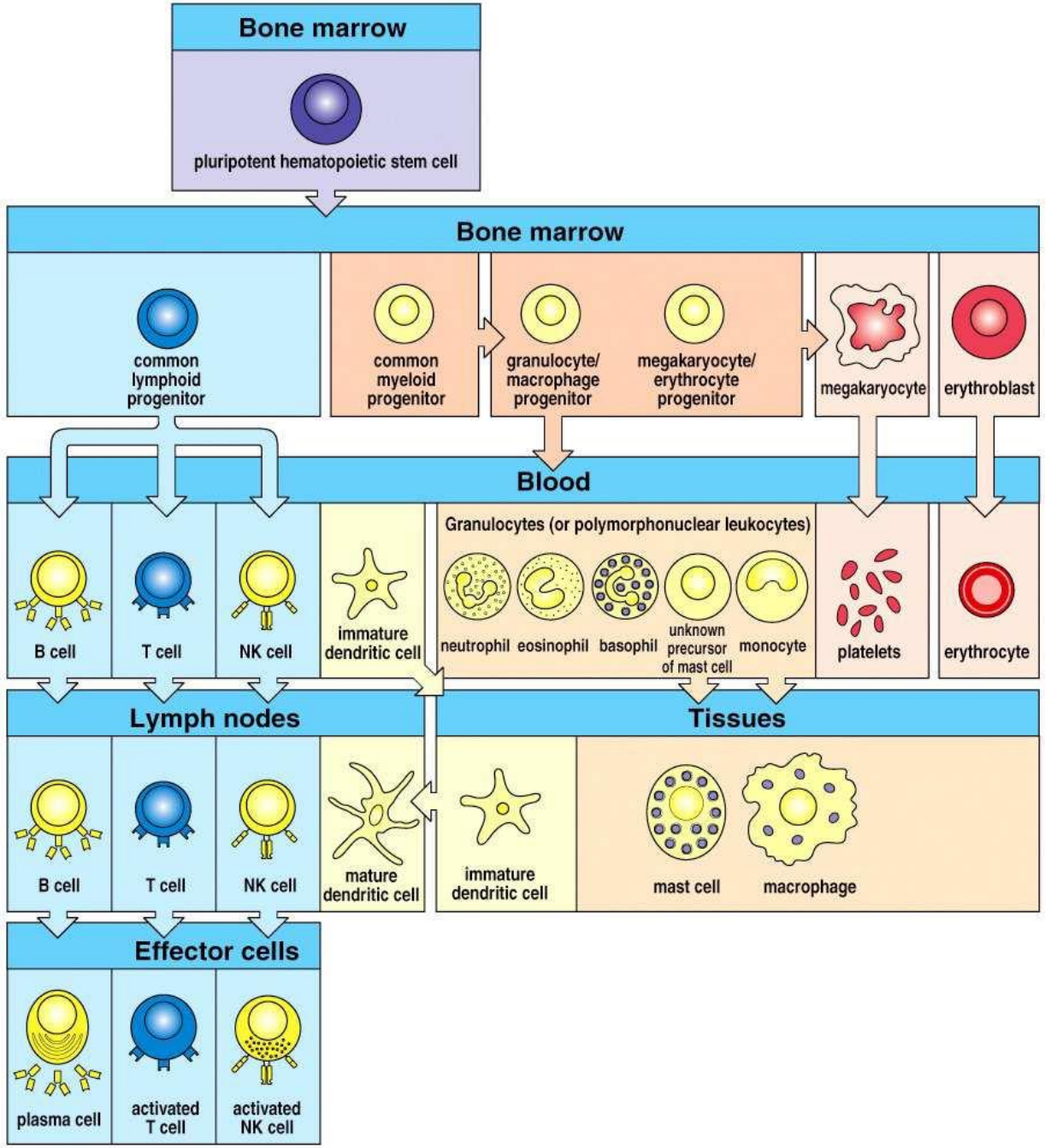


Figure 1-3 Immunobiology, 6/e. (© Garland Science 2005)

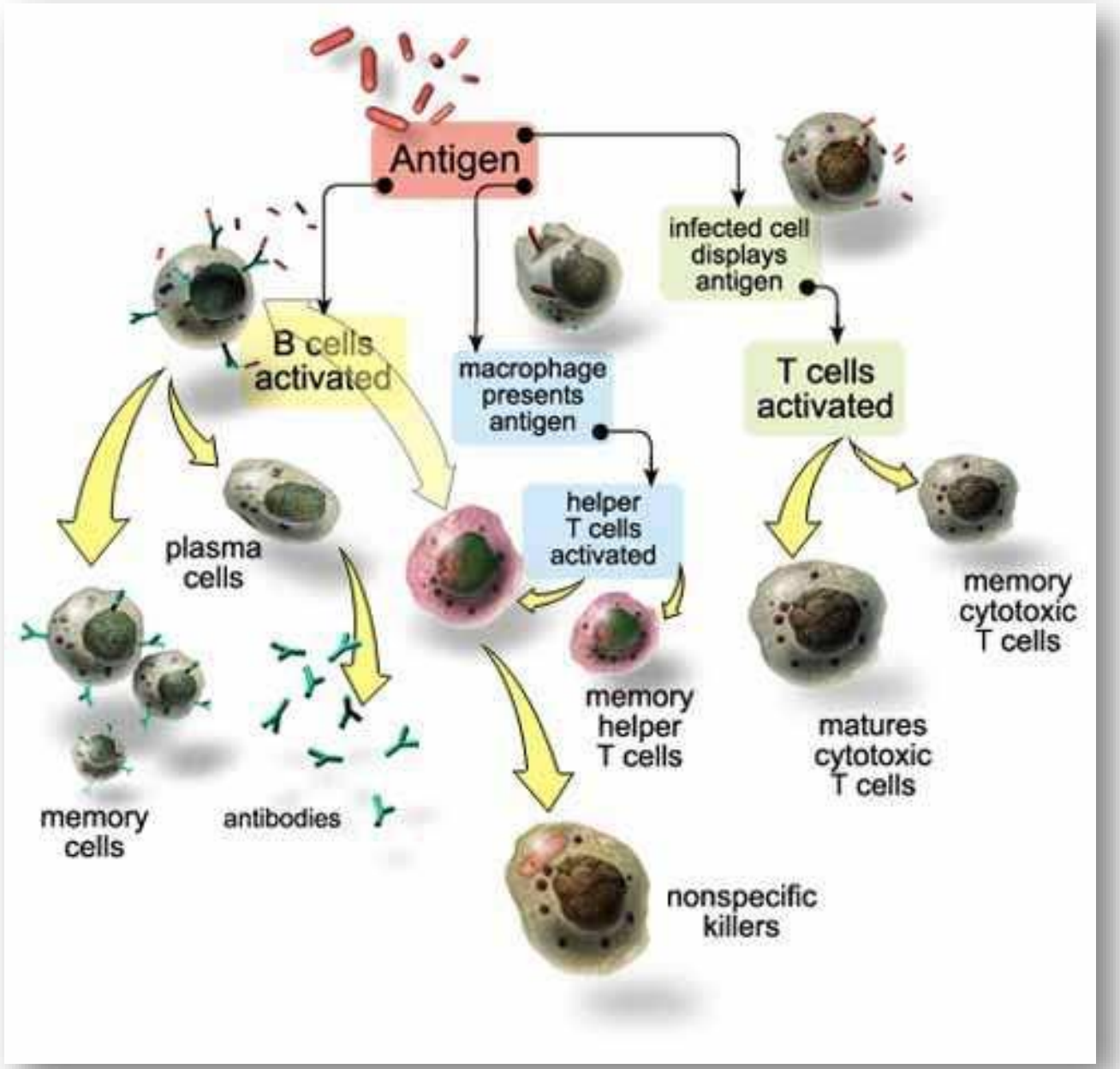
Progenitors

Innate immunity largely involves granulocytes and macrophages (although macrophages can influence adaptive immunity)

Adaptive immunity is mediated primarily by B and T lymphocytes

Other cells are regulatory or involved with both adaptive and innate immunity and/or are precursors of another cell type

Acquired Immune Responses



B cells
CD4+ T cells
CD8+ T cells

Adaptive (specific) defense 2 categories (both triggered by antigens)
- humoral (antibody mediated) immunity
- cellular (cell mediated) immunity

characteristics
- specific
- systemic
- memory

But if the body has all these defenses, why do so many people still get cancer?

Can tumour produce an immune response?

Evidence for Tumor Immunity

Spontaneous regression: melanoma, lymphoma

Regression of metastases after removal of primary tumor:

pulmonary metastases from renal carcinoma

Infiltration of tumors by lymphocytes and macrophages:

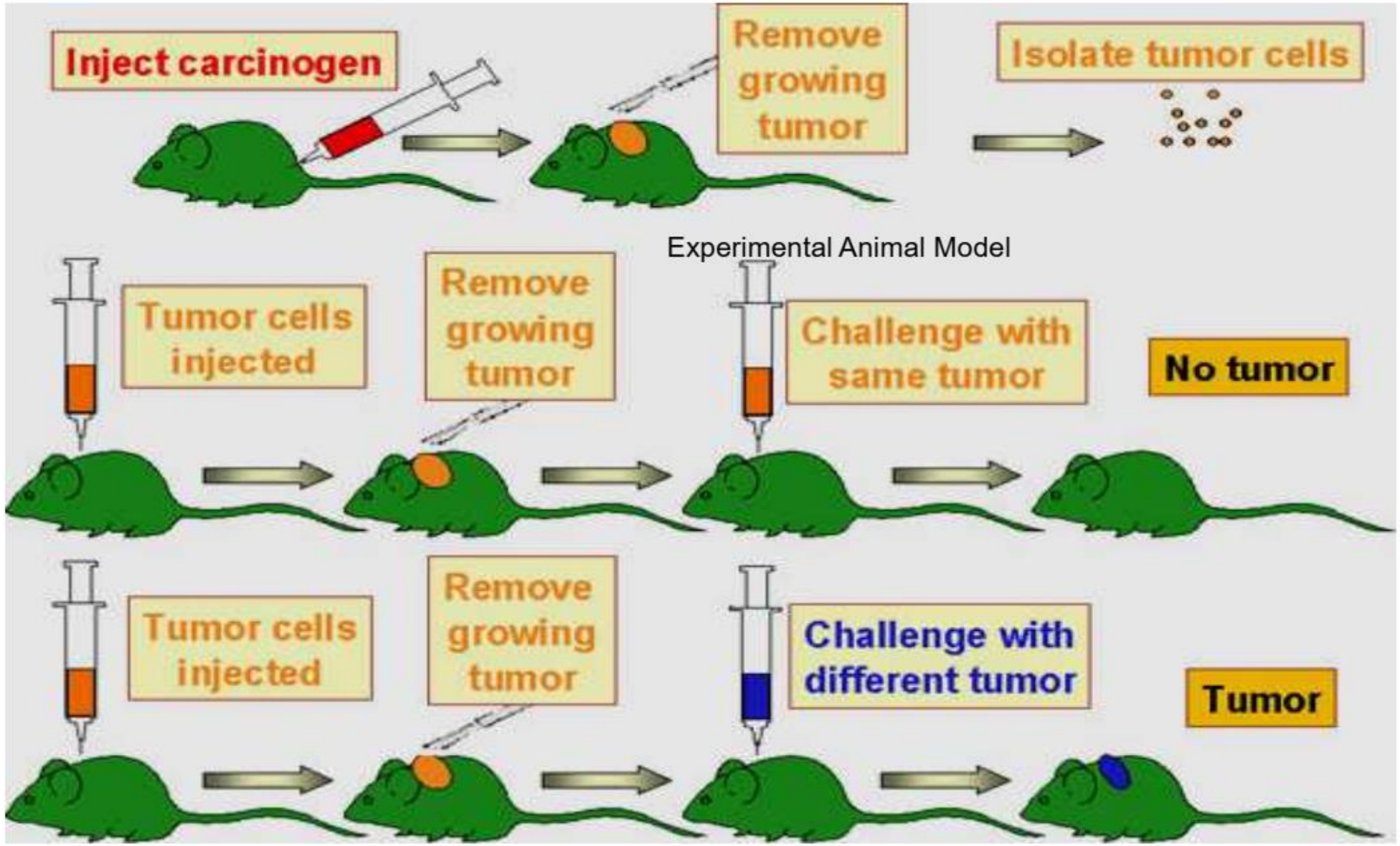
melanoma and breast cancer

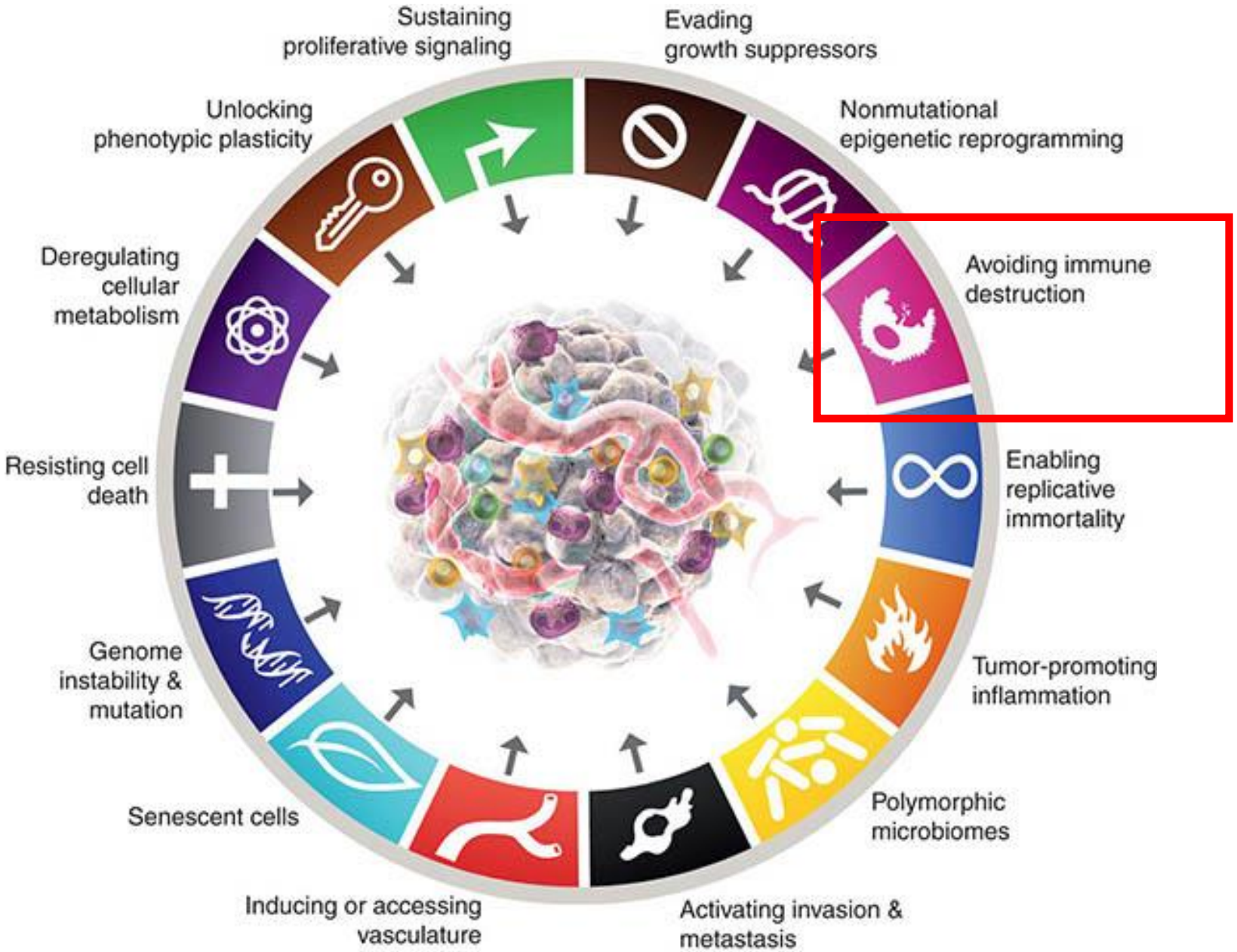
Lymphocyte proliferation in draining lymph nodes

Higher incidence of cancer after immunosuppression, immunodeficiency (AIDS)

Higher incidence in aged and neonates (less immunity)

Experimental Animal Model




Sustaining proliferative signaling
Evading growth suppressors
Unlocking phenotypic plasticity
Nonmutational epigenetic reprogramming
Deregulating cellular metabolism
Avoiding immune destruction
Resisting cell death
Enabling replicative immortality
Genome instability & mutation
Tumor-promoting inflammation
Senescent cells
Polymorphic microbiomes
Inducing or accessing vasculature
Activating invasion & metastasis

TUMOR IMMUNOLOGY

Cancer immune surveillance:

Immune system can recognize and destroy nascent transformed cells

Cancer Immunoediting:

Immune System kill and also induce changes in the tumor resulting in tumor escape and recurrence.

CANCER IMMUNOSURVEILLANCE

Cancer Immunosurveilance appears to be an important host protection process (a theory formulated in 1957 by Burnet) and that inhibits carcinogenesis and maintains regular cellular homeostasis

Cancer Immunosurveilance,- lymphocytes act as sentinels in recognizing and eliminating nascent transformed cells

Cancer immunity cycle.

In this cycle, tumor cells must release immunogenic tumor antigens for the priming and activation of tumor-specific T cells.

Tumor-reactive T cells must then infiltrate tumor tissue and recognize cancer cells in the context of a peptide-MHC complex to induce cancer cell death.

To evade immune mediated elimination, tumors must then develop strategies that disrupt this cycle.

Escape

Cancer immunomodeling

Immunity select for tumors with decreased antigenicity and/or immunogenicity and therefore, promote tumor outgrowth.

In this process termed "**cancer immunoediting**", cancer clones evolve to avoid immune-mediated elimination by leukocytes that have anti-tumor properties

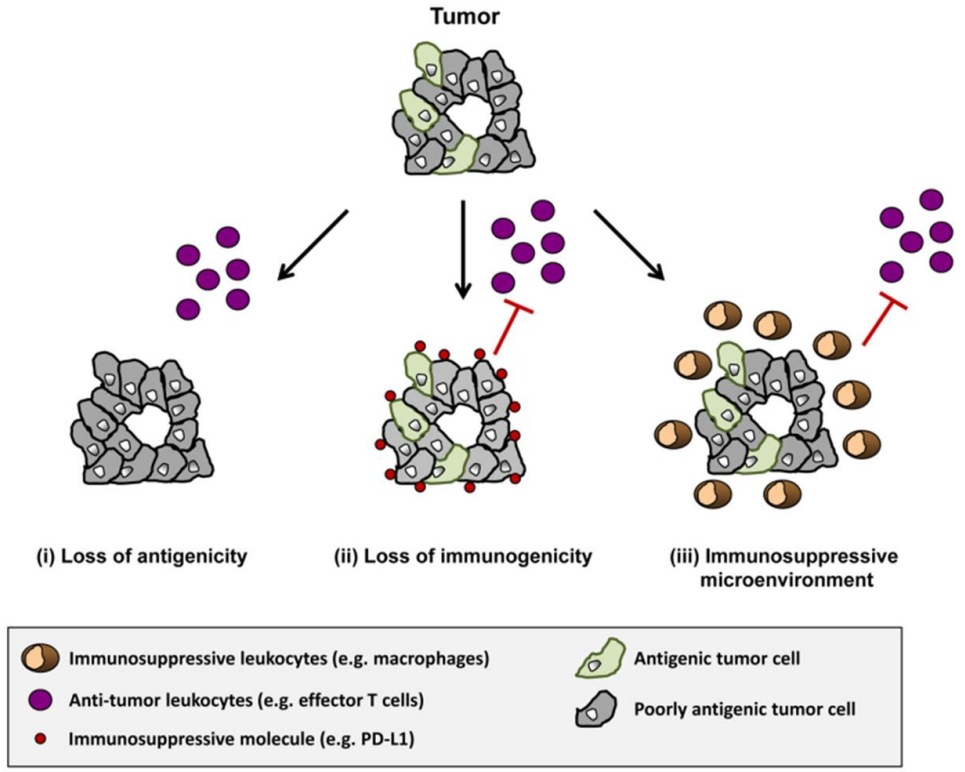
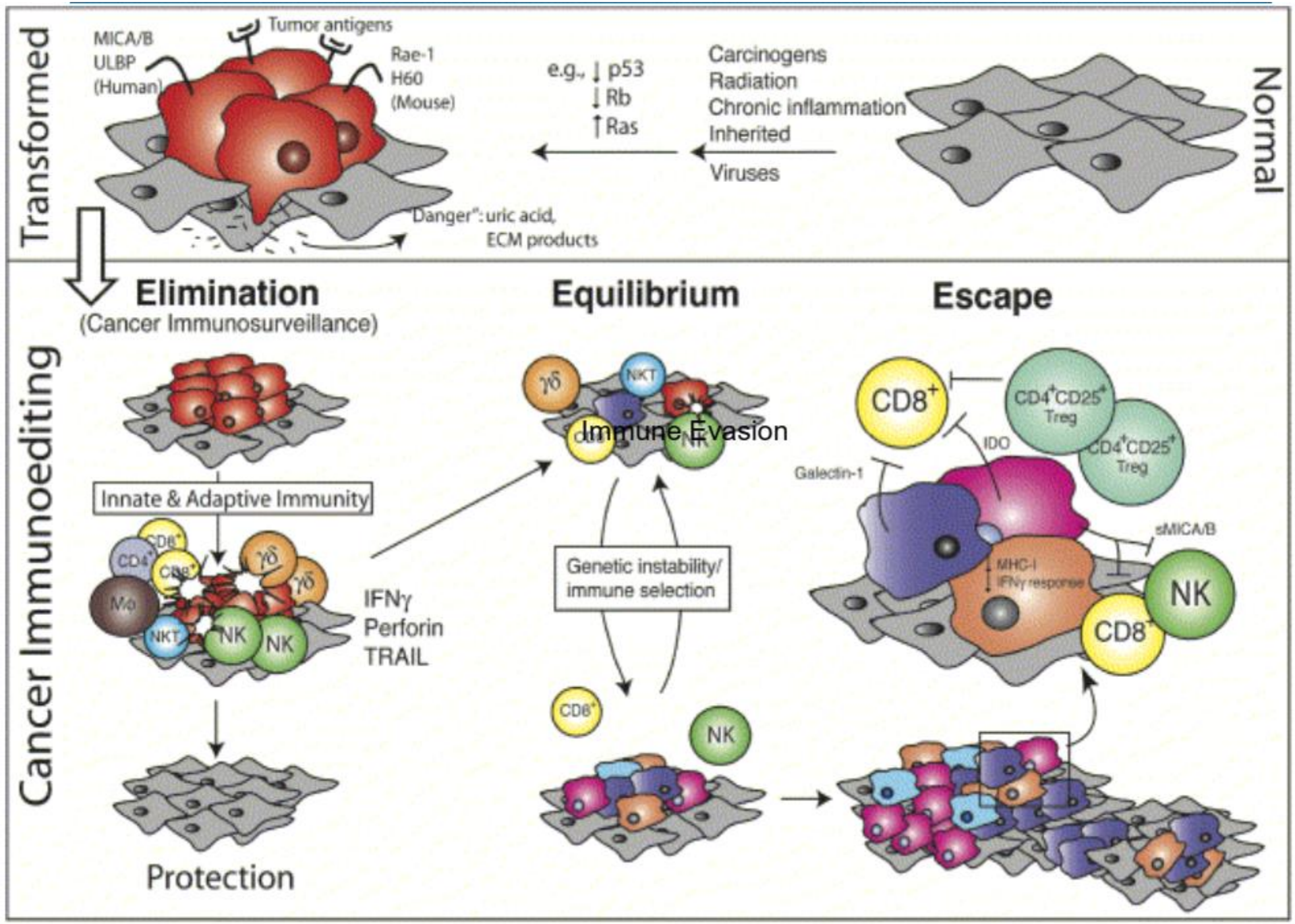


Figure 1. Immune escape mechanisms in cancer

Some tumors may also escape elimination by recruiting immunosuppressive leukocytes which orchestrate a **microenvironment** that spoils the productivity of an anti-tumor immune response


Transformed
MICA/B
ULBP
(Human)
Tumor antigens
Rae-1
H60
(Mouse)
e.g., ↓ p53
↓ Rb
↑ Ras
Carcinogens
Radiation
Chronic inflammation
Inherited
Viruses
Normal
"Danger": uric acid,
ECM products
Cancer Immunoediting
Elimination
(Cancer Immunosurveillance)
Innate & Adaptive Immunity
IFNγ
Perforin
TRAIL
Protection
Equilibrium
Immune Evasion
Genetic instability/
immune selection
Escape
CD8+
CD4+CD25+
Treg
IDO
Galectin-1
sMICA/B
MHC-I
IFNγ response
NK
CD8+

Antigenicity

The ability of the immune system to distinguish between normal and malignant cells is fundamental to cancer immunotherapy and relies, in part, on malignant cells retaining sufficient antigenicity. Tumors can express a variety of non-mutated and mutated antigens which have the potential to elicit tumor-specific immune responses .

However, to avoid immune-mediated elimination, cancer cells may lose their antigenicity. Loss of antigenicity can arise due to the immune selection of cancer cells which lack or mutate immunogenic tumor antigens as well as through the acquisition of defects or deficiencies in antigen presentation (e.g. loss of major histocompatibility (MHC) expression or dysregulation of antigen processing machinery)

Tumor antigens can be derived from viral proteins, proteins encoded by cancer-germline genes, differentiation antigens and proteins arising from somatic mutations or gene rearrangements

Immunogenicity

Tumors which retain sufficient antigenicity for immune recognition can escape elimination by decreasing their immunogenicity.

For example, IFN-γ produced by tumor infiltrating lymphocytes can induce the upregulation of the immunoinhibitory molecule PD-L1 on malignant cells . Across a variety of tumor types, membranous PD-L1 expression by tumor cells has been shown to strongly correlate with lymphocyte-rich regions of a tumor and with objective responses to anti-PD-1 antibody therapy .

These findings suggest that PD-L1 expression may be used to define a tumor that is responsive to immunotherapy.

However, not all PD-L1+ tumors are associated with immune infiltrates and some PD-L1+ tumors do not respond to anti-PD-1 immunotherapy.

Thus, additional markers of tumor immunogenicity will be needed which may involve other immune checkpoint molecules (e.g. galectin 9) expressed on tumor cells and surrounding stromal cells and/or the expression of negative regulatory markers present on tumor-infiltrating lymphocytes (e.g. PD-1, LAG-3, TIM-3, VISTA, CD244, CD160, and BTLA)

Tumor Microenvironment

Leukocyte infiltration into tumor tissue and recognition of malignant cells is necessary for successful immune mediated elimination.

However, significant variability in the leukocyte infiltrate can be seen across tumors of different tissue types. For example, effector T cells are observed to infiltrate tumor tissue in some solid malignancies such as melanoma and breast carcinoma, but are rarely observed to infiltrate other malignancies such as pancreatic ductal adenocarcinoma (PDAC).

While the immune response seen in each of these tumor types may initially act to inhibit tumor development, increasing evidence suggests that in some tumors, such as breast carcinoma and PDAC, tumor-infiltrating leukocytes may coordinate an active site of “immune privilege” which spoils the productivity of anti-tumor immunity

Some tumors may retain sufficient antigenicity and immunogenicity for recognition by tumor-specific T cells but evade immune elimination by orchestrating a suppressive microenvironment

Strategies to redirect the phenotype of the tumor microenvironment from immunosuppressive to immunostimulatory may hold promise for enhancing the efficacy of T cell immunotherapy

For tumors which retain sufficient antigenicity and immunogenicity, immunotherapy will need to focus on strategies that

1. boost tumor-specific immunity

(e.g. **vaccines**)

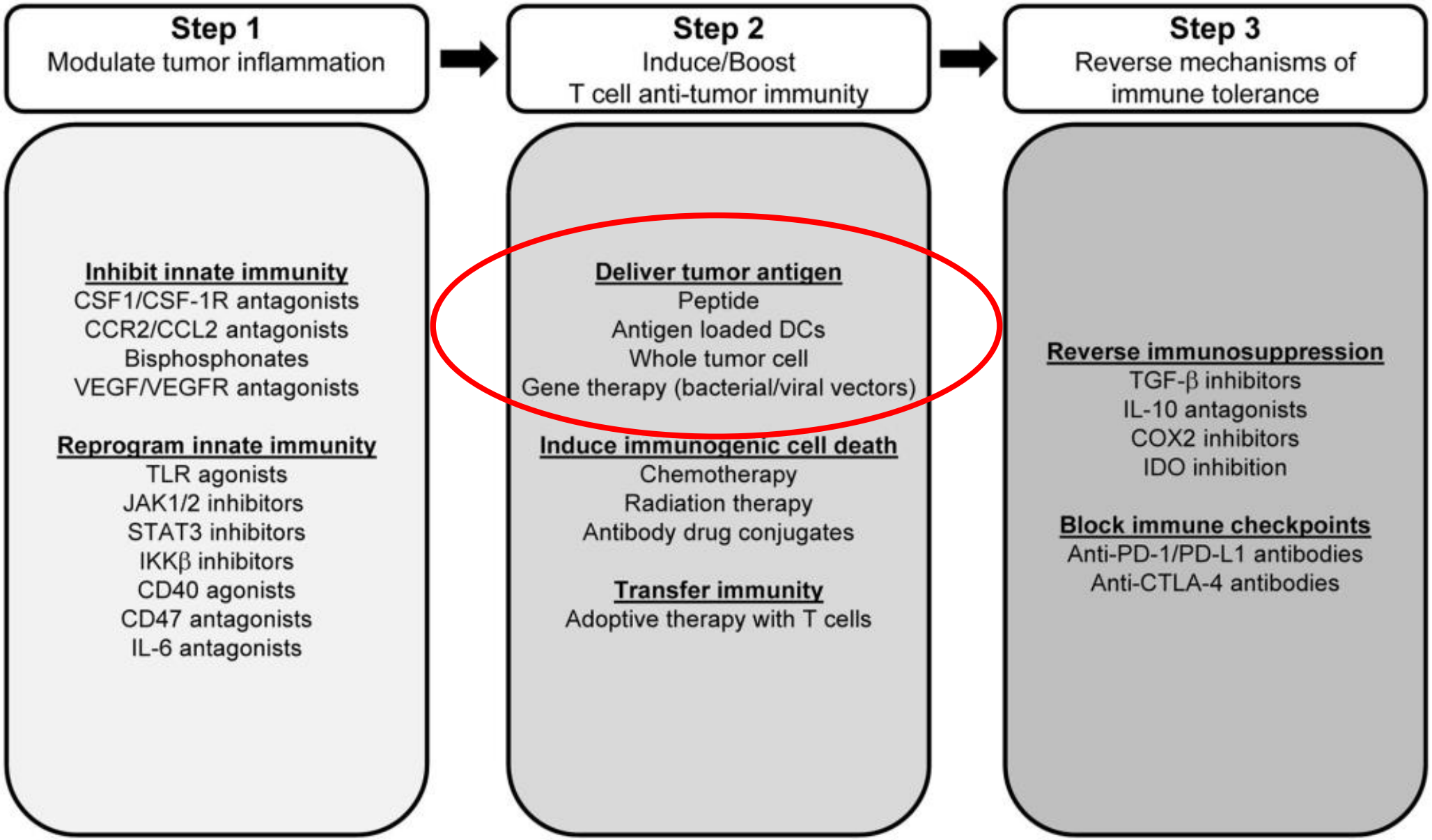
2.Enhance T cell killing of tumor cells

(e.g. immune checkpoint blockade using anti-CTLA-4 and anti-PD-L1/PD-1 antibodies)

Tumors which harbor defects in antigen processing and presentation and therefore, cannot be recognized by T cells.

For these tumors, strategies that re-direct innate immunity (e.g. NK cells or macrophages) with anti-tumor properties or alternatively, incorporate the adoptive cell therapy of T cells engineered to express chimeric antigen receptors **(CAR)** that recognize tumor specific proteins may be more effective due to their lack of dependency on MHC-restricted antigen presentation

For tumors dominated by immune suppressive cell populations with a weak lymphocyte infiltrate, so-called **“immune privileged”** tumors, strategies that dismantle immune suppression to permit the induction of tumor-specific T cells and their trafficking to tumors will be critical

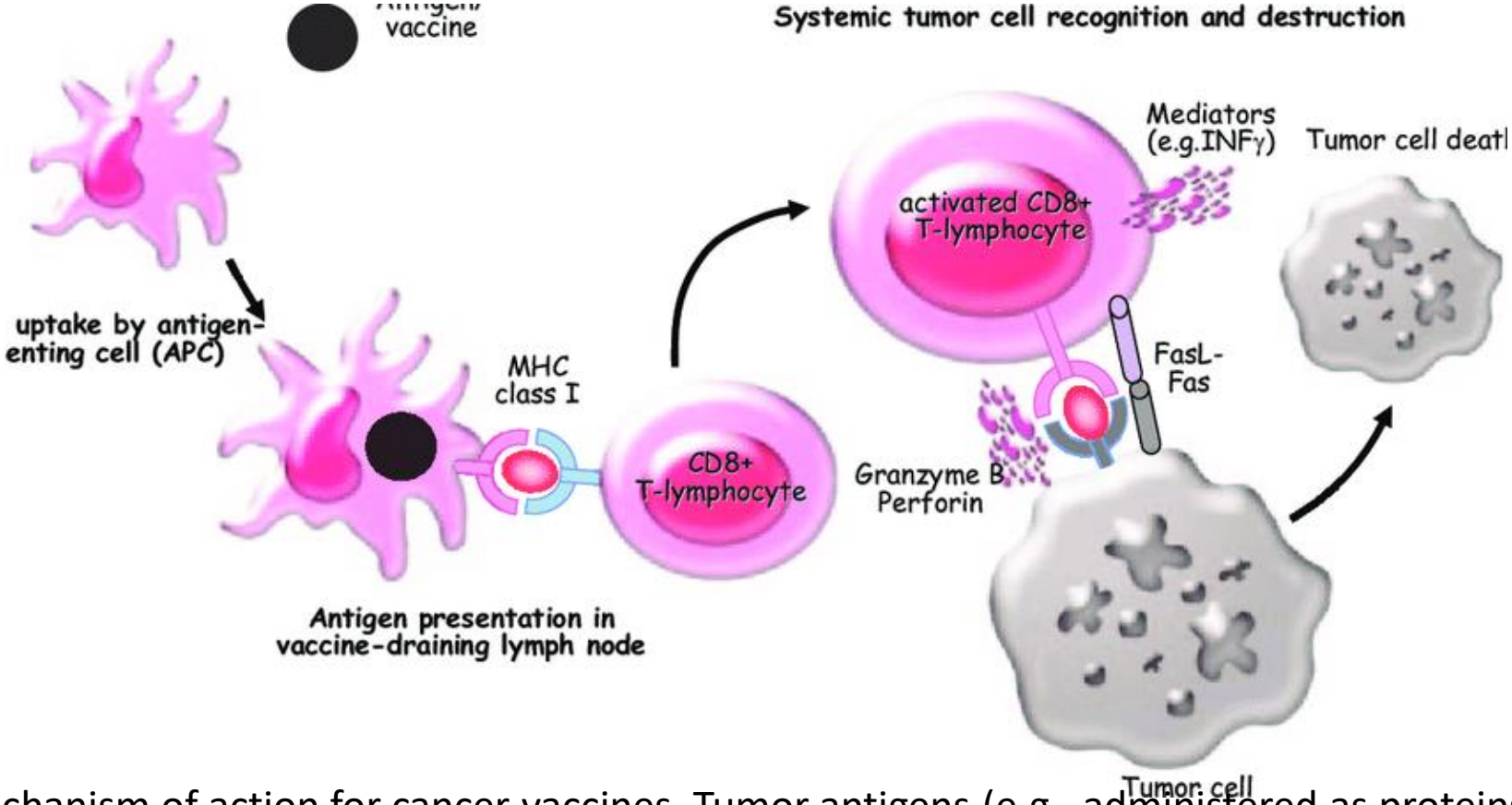

Step 1
Modulate tumor inflammation
Step 2
Induce/Boost
T cell anti-tumor immunity
Step 3
Reverse mechanisms of
immune tolerance
Inhibit innate immunity
CSF1/CSF-1R antagonists
CCR2/CCL2 antagonists
Bisphosphonates
VEGF/VEGFR antagonists
Reprogram innate immunity
TLR agonists
JAK1/2 inhibitors
STAT3 inhibitors
IKKβ inhibitors
CD40 agonists
CD47 antagonists
IL-6 antagonists
Deliver tumor antigen
Peptide
Antigen loaded DCs
Whole tumor cell
Gene therapy (bacterial/viral vectors)
Induce immunogenic cell death
Chemotherapy
Radiation therapy
Antibody drug conjugates
Transfer immunity
Adoptive therapy with T cells
Reverse immunosuppression
TGF-β inhibitors
IL-10 antagonists
COX2 inhibitors
IDO inhibition
Block immune checkpoints
Anti-PD-1/PD-L1 antibodies
Anti-CTLA-4 antibodies

Mechanism of cancer vaccines

Tumor antigens

Antigen selection is a critical process of cancer vaccines design. Tumor antigens recognized by T lymphocytes are central to the efficacy of cancer vaccines .

The ideal antigen for a cancer vaccine should be highly immunogenic, explicitly expressed in all cancer cells (not in normal cells) and necessary for the survival of cancer cells



Proposed mechanism of action for cancer vaccines. Tumor antigens (e.g., administered as proteins, peptides, or whole tumor cells) are taken up and processed by specialized antigen-presenting cells (APCs) such as dendritic cells (DCs). DCs migrate to the vaccine-draining lymph nodes and present relevant antigens to CD8 T lymphocytes, which, in turn, are able to recognize tumor cells throughout the body and destroy them by several effector mechanisms such as the perforin/granzyme pathway, direct cell-cell interaction (e.g., Fas/Fas ligand), or certain mediators (e.g., INF). Not shown but also of importance are B lymphocytes, CD4 T helper cells and cells of the innate immune system such as natural killer cells and macrophages. Abbreviations: INF, interferon; MHC, major histocompatibility complex

Tumor antigens

TAAs
(Tumour associatrd antigens)

TSAs
(Tumour specific antigens)

TAAs

TAAs also be known as tumor-shared antigens. TAAs include “self-antigens” such as differentiated antigens, overexpressed antigens, cancer-testicular antigens, and viral-original “non-self” antigens

Prominent examples of overexpressed tumor antigens are human epidermal growth factor receptor 2 (HER2) and human telomerase reverse transcriptase.

Tissue differentiation antigens are expressed by tumor cells and normal cells of the same tissue origin as tumor cells, such as prostate-specific antigen (PSA) expressed in the prostate gland and prostate cancer melanoma antigens tyrosinase expressed by normal melanocytes, and melanoma cells

TSAs

TSAs are a class of proteins specifically expressed in tumor cells. TSAs are mentioned as **neoantigens** sometimes. The individual-specific non-autogenous proteins produced due to mutations in tumor cells are called neoantigens. Neoantigens are expressed only by tumor cells, triggering a valid tumor-specific T-cell response with limited “off-target” damage .

Compared with TAAs, neoantigens have more potent immunogenicity and higher major histocompatibility complex (MHC) affinity. What’s more, they are unaffected by central immune tolerance

Cancer vaccines targeting **neoantigen** have become the main direction of tumor vaccine in recent years.

Recently, several clinical trials evaluating **neoantigen** vaccines have yielded promising results with improved patient survival .

An mRNA neoantigen melanoma vaccine is a typical example that induced T cell infiltration and neoantigen-specific killing of autologous tumor cells . The incidence of metastatic events was significantly reduced after vaccination, resulting in sustained progression-free survival

Besides, the neoantigen-loaded DC vaccination could provoke a cell-specific response that led to antigen spreading in patients with melanoma

The high-quality neoantigens should be associated with the following features:

First: They should manifest strong binding affinity to human leukocyte antigen (HLA);

Second: They should be highly heterologous compared to the wild type;

Third: They can be expressed by most tumor cells;

Fourth; They are generated as the consequences of mutations that affect survival.

The neoantigens with these features could induce a robust immune response and prevent the development of tumor-immune escape

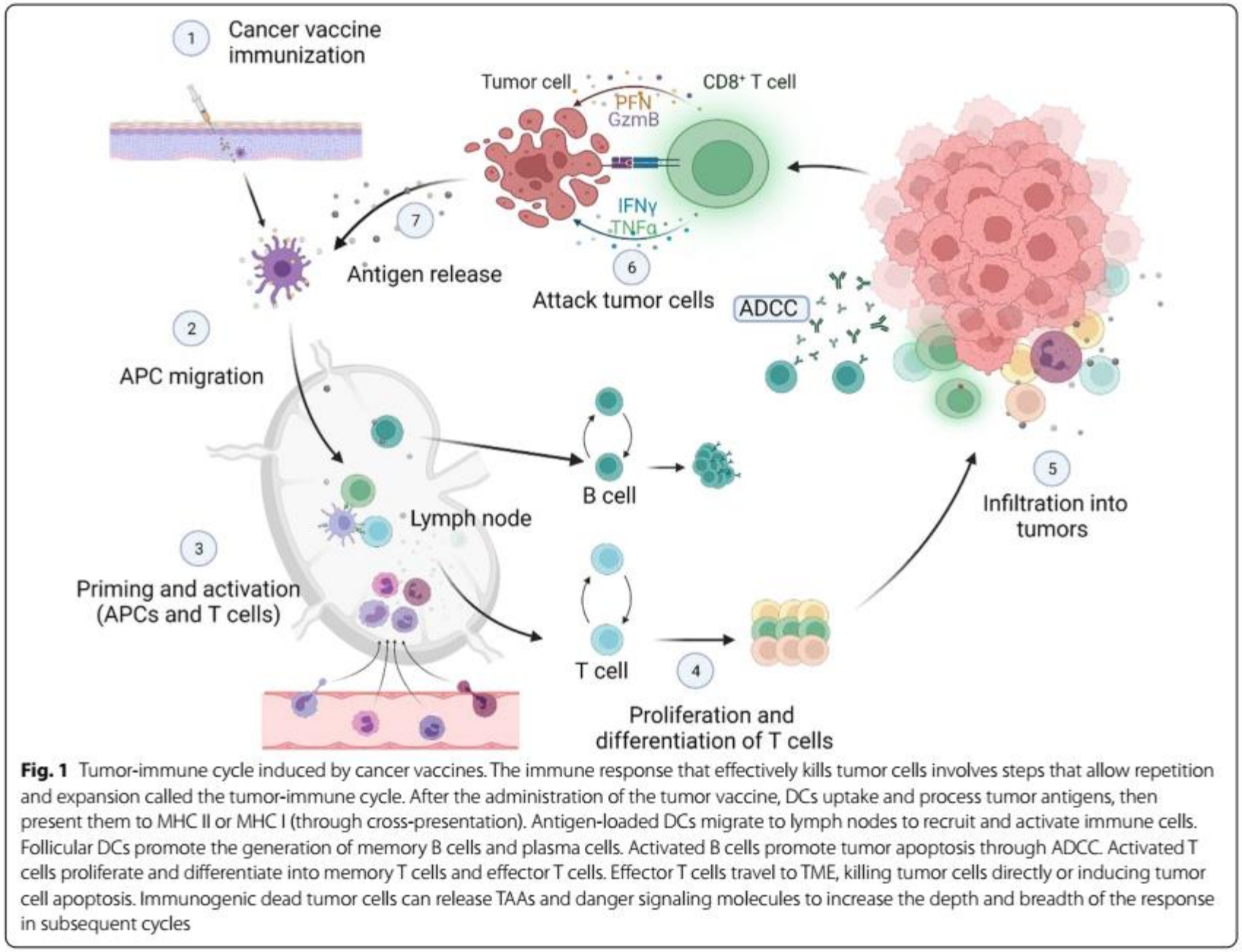


Fig. 1 Tumor-immune cycle induced by cancer vaccines. The immune response that effectively kills tumor cells involves steps that allow repetition and expansion called the tumor-immune cycle. After the administration of the tumor vaccine, DCs uptake and process tumor antigens, then present them to MHC II or MHC I (through cross-presentation). Antigen-loaded DCs migrate to lymph nodes to recruit and activate immune cells. Follicular DCs promote the generation of memory B cells and plasma cells. Activated B cells promote tumor apoptosis through ADCC. Activated T cells proliferate and differentiate into memory T cells and effector T cells. Effector T cells travel to TME, killing tumor cells directly or inducing tumor cell apoptosis. Immunogenic dead tumor cells can release TAAs and danger signaling molecules to increase the depth and breadth of the response in subsequent cycles

Stimulation of anti-tumor immunity

Cancer vaccines platforms

Cancer vaccines can be divided into four categories:

1.cell-based vaccines,

2. peptide-based vaccines,

3. viral-based vaccines,

4.nucleic acid-based vaccines

Cell based vaccines

Cell based vaccines are the form of cancer vaccines initially developed .

Cell-based cancer vaccines are often prepared from whole cells or cell fragments, containing almost tumor antigens, inducing a broader antigen immune response.

DC vaccine is an important branch of cell-based vaccines. Personalized neoantigen cancer vaccines based on DC have shown promising anti-tumor effects in clinical trials. However, the cumbersome process and expensive cost limit the development of DC vaccines.

Viral-based vaccines

Viruses are naturally immunogenic and their genetic material can be engineered to contain sequences encoding tumor antigens.

Several recombinant viruses, such as adenovirus, can infect immune cells as vectors. The engineered virus vaccines can present tumor antigens in large quantities in the immune system and produce anti-tumor immunity.

Furthermore, the oncolytic virus can be used as a vector as well. Except for providing tumor antigens, the virus itself can also lyse the tumor, release tumor antigens, further increase the vaccine’s effectiveness, and produce long-term immune memory

Peptide-based subunit vaccines

Peptide-based subunit vaccines, including chemical and biosynthetic preparations of predicted or known specific tumor antigens, induce a robust immune response against the particular tumor antigen site.

Peptide-based subunit vaccine combined with adjuvants can efficiently provoke humoral immune response, suitable for preventing and treating viral infectious diseases.

HBV and HPV vaccines for liver and cervical cancers were primarily peptide-based subunit vaccines. Especially, virus-like particles (VLP)-based subunit vaccines that can activate cellular immune responses have shown good antitumor activity in recent years.

The nucleic acid vaccine

The nucleic acid vaccine is a promising vaccine platform. The nucleic acid vaccine induces strong MHC I mediated CD8+T cell responses; thus, it is a desirable cancer vaccine platform .

Nucleic acid vaccines can simultaneously deliver multiple antigens to trigger humoral and cellular immunity.

Additionally, nucleic acid vaccines can encode full-length tumor antigens, allowing APC to cross-present various epitopes or present several antigens simultaneously. Finally, the nucleic acid vaccine preparation is simple and fast, which is suitable for developing personalized **neoantigen** cancer vaccines

Therapeutic Cancer Vaccines

- **Bacillus Calmette-Guérin (BCG):** a vaccine that uses weakened bacteria to stimulate the immune system; approved for patients with early-stage bladder cancer.

- **Sipuleucel-T (Provenge®):** a vaccine composed of patients' own stimulated dendritic cells; approved for prostate cancer.

Table 2 | **In situ vaccine candidates under clinical consideration as monotherapies or in combination**

Receptor	Agonist	Clinical trial identifier	Route[a]	Treatment	Condition
TLR and STING agonists					
RIG-I/MDA5 and TLR3	Poly-ICLC	NCT02423863	IT + IM	Poly-ICLC + anti-PD1 or anti-PDL1	Melanoma, H&N cancer, sarcoma, non-melanoma skin cancers
		NCT02643303	IT + IM	Poly-ICLC + anti-CTLA-4 and anti-PDL1	Advanced, measurable, biopsy-accessible cancers
TLR4	Glucopyranosyl lipid A (G100)	NCT02501473	IT	G100 + pembrolizumab	Follicular low-grade NHL
		NCT03915678	IT	G100 + atezolizumab + radiotherapy	Multiple solid tumours
		NCT02406781	IT	G100 + pembrolizumab + cyclophosphamide	Sarcoma
TLR7/8	NKTR-262	NCT03435640	IT	NKTR-262 + NKTR-214 (CD122 agonist) + nivolumab	Multiple cancers
TLR9	CpG ODN SD-101	NCT02927964	IT	Radiotherapy + SD-101 + ibrutinib	Lymphoma
		NCT02521870	IT	SD-101 + pembrolizumab	Melanoma and H&N cancer
	(VLP) encapsulated-TLR9 agonist CMP-001	NCT03084640	SC	CMP-001 + pembrolizumab	Melanoma
		NCT03618641	SC + IT	CMP-001 + nivolumab	Melanoma
		NCT02680184	IT	CMP-001 ± pembrolizumab	Melanoma
		NCT03983668	IT	CMP-001 ± pembrolizumab	R/R lymphoma
		NCT03438318	SC + IT	CMP-001 + atezolizumab ± radiotherapy	NSCLC
		NCT03507699	SC + IT	CMP-001 + nivolumab + ipilimumab ± radiotherapy	Metastatic CRC with liver metastases
STING	MK-1454	NCT03010176	IT	MK-1454 ± pembrolizumab	Solid tumours and lymphoma
	E7766	NCT04109092	IT	Monotherapy	Bladder cancer
	ADU-S100	NCT03937141	IV	ADU-S100 + pembrolizumab	H&N cancer
		NCT03172936	IT	ADU-S100 + anti-PD1	Solid tumours and lymphoma
		NCT02675439	IT	ADU-S100 + ipilimumab	Solid tumours and lymphoma
	BMS-986301	NCT03956680	ND	BMS-986301 + nivolumab + ipilimumab	Advanced solid cancers
	SB-11285	NCT04096638	IV	SB-11285 ± nivolumab	Advanced solid cancers
FLT3L and CD40 agonists					
rhFLT3L	CDX-301	NCT02129075	SC	Poly-ICLC + CDX-1401 ± CDX-301	Stage IIB–IV melanoma
		NCT03789097	ND	CDX-301 + poly-ICLC + pembrolizumab + radiotherapy	NHL, metastatic breast cancer, H&N squamous cell carcinoma
		NCT01976585	IT	CDX-301 + poly-ICLC	Low-grade BCL
		NCT02839265	SC	CDX-301 + SBRT	NSCLC
Agonistic anti-CD40 antibody	APX005M	NCT02482168	IV	Monotherapy	Multiple solid cancers
	CDX-1140	NCT03329950	ND	CDX-1140 ± CDX-301 (rhFLT3L) ± pembrolizumab	Multiple cancers
	SEA-CD40	NCT02376699	IV or SC	SEA-CD40 + pembrolizumab + chemotherapy	Solid tumours and Lymphoma
Oncolytic virus, TVec					
Modified HSV-1	TVec	NCT02263508	IT	Tvec ± pembrolizumab	Melanoma
		NCT03802604	IT	Tvec + atezolizumab	Breast cancer
		NCT03256344	IT	Tvec + atezolizumab	Breast cancer and CRC
		NCT02509507	IT	Tvec + pembrolizumab	Multiple cancers
		NCT04185311	IT	Tvec + nivolumab + ipilimumab	Breast cancer

THANK YOU

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