14) Tumor Immunology 2

I. The Immune System Overview

The immune system is divided into two primary branches that work together to monitor tissues and identify damaged or cancerous cells.

- **Innate Immunity**: This is the pre-existing, first line of defense that responds rapidly to infection or cancer. It is non-selective ("kill first, ask later") and includes cells like macrophages, neutrophils, and Natural Killer (NK) cells.
- **Adaptive Immunity**: This system is selective and "educated," meaning it can "learn" to recognize specific stimuli. It includes B cells (which produce antibodies) and T cells (CD4^{+} helper and CD8^{+} cytotoxic). It features long-lasting memory to recall prior exposures.

II. Tumor Development and Immune Evasion

Tumors form due to various genetic and environmental factors, such as UV radiation damaging DNA in melanocytes, which leads to melanoma. While the immune system initially attacks tumors using NK cells and cytotoxic T cells—which release **perforin** and **granzymes** to punch holes in the cell surface and induce **apoptosis**—tumors often evolve to survive.

- **Immuno-editing**: Tumors are often heterogeneous. As the immune system kills recognizable cells, those it cannot sense survive and become more prevalent, leading to the emergence of a tumor that cannot be detected by the immune system.
- **Immune Checkpoints**: Some tumor cells actively suppress T cells by expressing inhibitory molecules like **PD-L1**. PD-L1 binds to the **PD-1** receptor on T cells and deactivates them, creating an immune checkpoint.
- **Immunosuppressive Environment**: Tumors can attract immune cells that suppress the activity of other immune cells, such as **regulatory T cells** and certain myeloid cells, thereby supporting tumor growth.

III. Cancer Immunotherapy Strategies

Immunotherapy involves using the body's own immune system to fight cancer by activating immune cells to recognize cancer tissue as different from normal body cells.

1. **Non-Specific Immune Stimulation**: This approach provides a general boost to the immune system *in vivo*.
    - **Cytokines**: Drugs like **IL-2** and **IFNα** (Interferon alpha) are signaling molecules used to boost the activity of anti-tumor immune cells.
    - **BCG Vaccine**: A weakened live bacterium primarily used for tuberculosis. When injected directly into the bladder, it causes inflammation that increases the number of immune cells around bladder cancer.
2. **Immune-Checkpoint Blockade**: These therapies remove the "brakes" (blockades) that dampen the immune response to make it stronger against cancer.
    - **Anti-CTLA-4**: Molecules like the antibody **Ipilimumab** block CTLA-4, helping dendritic cells drive anti-tumor T cell responses.
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    - **Anti-PD-1**: Antibodies that bind to PD-1 stop this molecule from switching off cytotoxic T cells.
3. **Adoptive Cell Transfer (ACT)**: This involves extracting immune cells from the patient, activating or modifying them *outside* the body, and then reintroducing them.
    - **Tumor-derived cells**: These cells are difficult to extract in large numbers, but they have already learned to recognize the specific tumor.
    - **CAR T-cell Therapy**: T cells are taken from the blood and genetically engineered with **Chimeric Antigen Receptors (CAR)** to specifically react to and attack cancer cells.
4. **Vaccination Strategies**: Unlike general stimulation, these direct immune cells specifically to the cancer tissue.
    - **Viral Vaccines**: Weakened versions of viruses (e.g., modified **HSV**) are engineered to produce immune-stimulating factors against specific cancers like melanoma.
    - **Tumor Cell Vaccines**: A patient's own tumor cells are extracted, irradiated (to stop spreading), and engineered to secrete growth factors that alert the immune system before being reinjected.
    - **APC Vaccination**: Dendritic cells (Antigen Presenting Cells) are taken from the patient, matured outside the body, and loaded with tumor antigens. When reintroduced, they help the immune system recognize the tumor (e.g., **Sipuleucel-T** for prostate cancer).

Cancer Immunotherapy Strategies Table

Strategy	Mechanism of Action	Key Examples / Agents
Non-Specific Stimulation	Provides a general boost to the immune system *in vivo* to alert and activate cells like APCs and T cells.	**IL-2**, **IFNα**; **BCG Vaccine** (for bladder cancer).
Checkpoint Blockade	Removes inhibitory "blockades" (like CTLA-4 or PD-1) that tumors use to switch off T cells.	**Ipilimumab** (Anti-CTLA-4); **Nivolumab/Pembrolizumab** (Anti-PD-1).
Adoptive Cell Transfer	Extracts immune cells to activate or genetically engineer them outside the body before reintroduction.	**CAR T-cell Therapy**; Tumor-Infiltrating Lymphocytes.
Vaccination Strategies	Uses antigens, modified viruses, or engineered cells to direct the immune system specifically to cancer tissue.	**Sipuleucel-T** (APC vaccine); Modified **HSV** (Viral vaccine).