13) Tumor immunology 1

I. Fundamental Principles of Tumor Immunology

- **Immune Surveillance:** The immune system (innate and adaptive) recognizes and reacts against many tumors. This is evidenced by the increased incidence of tumors in immunocompromised individuals.
- **Tumor Antigens:** Although derived from host cells, tumors elicit immune responses because they express antigens perceived as foreign.
    - **Mutated genes:** Products of mutated **oncogenes** or **tumor suppressor genes** (e.g., p53, RAS).
    - **Overexpressed proteins:** Normal proteins expressed at abnormally high levels.
    - **Oncofetal antigens:** Proteins normally silent in adults but expressed in tumors.
    - **Viral products:** Antigens from oncogenic viruses.

II. Immune Effector Mechanisms

1. Adaptive Immunity (The Principal Defense)

- **CD8+ Cytotoxic T Lymphocytes (CTLs):** These are the **principal mechanism** of adaptive tumor immunity. They kill tumor cells after recognizing tumor-specific peptides.
- **Cross-Priming:** CD8+ T cell responses are often induced when professional **antigen-presenting cells (APCs)** ingest tumor cells and present their antigens to T cells.
- **CD4+ Helper T Cells:** Provide cytokines (like **TNF** and **IFN-γ**) that increase tumor sensitivity to lysis and activate macrophages.

2. Innate Immunity

- **NK Cells:** Kill tumor cells that have **reduced class I MHC expression** or those coated with IgG antibodies (**ADCC**).
- **Macrophages: M1 macrophages** inhibit tumors through TNF and reactive oxygen species. Conversely, **M2 macrophages** may promote tumor growth and angiogenesis by secreting **VEGF** and **TGF-β**.

III. Immune Evasion by Tumors

Tumors often "overwhelm" the immune system through several strategies:

1. **Immune Checkpoints:** Tumors exploit inhibitory pathways like **CTLA-4** and **PD-1** to deactivate T cells.
2. **Antigen Loss:** Some tumors stop producing the target antigen or mutate **MHC genes** to avoid recognition.
3. **Immunosuppressive Environment:** Tumors secrete proteins like **TGF-β** and recruit **Regulatory T cells (Tregs)** or **Myeloid-derived suppressor cells (MDSCs)** to inhibit immune attacks.

4. **Lack of Costimulation:** Most tumor cells do not express the necessary "second signals" (**costimulators**) to activate T cells.

IV. Cancer Immunotherapy

1. Major Forms

- **Checkpoint Inhibitors:** Monoclonal antibodies that block **PD-1/PD-L1** or **CTLA-4**, essentially "releasing the brakes" on the immune system.
- **CAR T Cell Therapy:** T cells are genetically engineered to express **Chimeric Antigen Receptors (CARs)**.
    - **Mechanism:** CARs recognize surface antigens (like **CD19** or **BCMA**) **independently of MHC**.
    - **Challenges:** Severe side effects include **cytokine release syndrome** and neurotoxicity.
- **Others:** Cancer vaccines, oncolytic virus therapy, and targeted antibodies.

2. Immune-Related Adverse Events (irAEs)

Therapy can cause the immune system to attack healthy tissue, leading to:

- **Tissue-specific autoimmune reactions.**
- Increased **inflammatory cytokines** and **autoantibodies**.
- Interestingly, the presence of irAEs is often associated with better **clinical efficacy** (higher response rates and survival).

V. Key Biomarkers and Immunotypes

Feature	Description	Clinical Significance
PD-L1 Expression	High levels of PD-L1 on tumor cells.	Predicts higher likelihood of response to PD-1 inhibitors.
Tumor Mutational Burden (TMB)	The total number of mutations in a tumor.	High TMB predicts better response to checkpoint immunotherapy.
Immune Inflamed	Tumor is abundant with immune cell infiltrates.	Often responsive to immunotherapy but T cells are "braked".
Immune Excluded	T cells are present only in the stroma (edges), not the tumor.	T cells are blocked from penetrating the tumor.
Immune Desert	No T cells are present in or around the tumor.	Generally poor response to current immunotherapies.
Gut Microbiome	Composition of bacteria in the gut.	Diverse gut bacteria are associated with better treatment response.