TOPIC : EVASION OF IMMUNE SURVEILLANCE

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1. Immune Surveillance Theory: The immune system can detect and eliminate tumor cells. Evidence includes lymphocytic infiltrates in tumors, higher cancer rates in immunodeficient hosts, and detection of tumor-specific immune responses.

2. Types of Tumor Antigens: Tumors express:

    a. Neoantigens (from driver/passenger mutations),

    b. Overexpressed self-proteins (e.g., tyrosinase in melanoma),

    c. Aberrantly expressed antigens (e.g., MAGE proteins),

    d. Viral oncogenic proteins (e.g., HPV E6/E7, EBV proteins).

3. CD8+ Cytotoxic T Lymphocytes (CTLs): Main antitumor effectors. They recognize tumor antigens on MHC I and directly kill tumor cells. Their activation depends on antigen presentation and co-stimulation by APCs.

4. Cross-Presentation: Dendritic cells present extracellular antigens on MHC I to activate CD8+ T cells. This is crucial in initiating antitumor immunity from dead tumor cell debris.

5. Other Immune Effector Cells:

    a. CD4+ Th1 cells enhance CTL function via IFN-γ.

    b. Natural Killer (NK) cells target MHC I-deficient tumors.

    c. Activated macrophages destroy tumors using ROS, nitric oxide, and TNF-α.

6. CAR-T Cell Therapy: CTLs are genetically modified to express chimeric antigen receptors (CARs) for specific tumor targets (e.g., CD19 in B-cell malignancies). CAR-T cells bypass MHC restriction and provide long-term control.

7. Tumor Immune Evasion Strategies:

    a. Selective survival of antigen-negative variants.

    b. Downregulation or loss of MHC I.

c. Upregulation of immune checkpoint ligands (PD-L1, CTLA-4).

d. Secretion of suppressive factors (TGF-β, IL-10, PGE2, VEGF).

e. Induction of regulatory T cells (Tregs).

8. Checkpoint Inhibition Therapy: Antibodies against PD-1, PD-L1, or CTLA-4 restore T cell activity. These therapies are most effective in tumors with high mutation burden (e.g., MMR-deficient cancers).

9. Challenges & Toxicities: Only 25–40% of tumors respond. Toxicities include autoimmune colitis, thyroiditis, myocarditis, pneumonitis, and dermatitis—often requiring immunosuppressive therapy or stopping treatment.

10. Future Directions: Personalized therapy based on dominant immune escape mechanisms in each tumor is critical. Combination therapies (e.g., anti–PD-1 + anti–CTLA-4) offer better outcomes than monotherapy and are under active clinical trial evaluation.