General features of tumor immunity and escape mechanisms

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Induction of Tumor Adaptive Immunity requires that Cancer Cell-Derived Antigens be Presented and Recognized as “Foreign” by Specific Clones of Naïve T cells.
Tumor Cells Become Visible to T Lymphocytes

a Antigens: high tumour specificity
- Mutation
  - Most tumours
  - Tumour-specific expression
    - Many tumours
    - Tissue-specific expression
    - Melanomas

b Antigens: low tumour specificity
- Overexpression
  - Some tumours

Neoantigens
- Spermatocytes
- Spermatogonia
- Trophoblasts
- Other normal cells
- Melanocytes
- Other normal cells

Coulie PG et al., Nat Rev Cancer, 2014
Neoantigens as a Product of Genomic Instability

Evolution of clonal populations

MRCA=most recent common ancestor

Normal cell → MRCA cell

Time point X: diagnosis and treatment initiation

Time point Y: distant and local relapse

Distant metastasis

Routes to genomic instability

M phase genes involved in:
- Chromosome condensation
- Sister chromatid cohesion
- Kinetochore structure
- Centrosome and microtubule formation

Aneuploidy

CIN

Telomere dysfunction

Genomic instability

Error prone repair pathways, e.g. NHEJ and SSA

Mismatch repair gene dysfunction, e.g. MSH2 and MLH1

Many single-base substitutions (14–40 Mb⁻¹)
Small indels at polymorphic tracts (5–12 Mb⁻¹)

Homologous repair deficiency, e.g. mutant BRCA1, BRCA2 and PALB2

Mutagenic exposures, e.g. ultraviolet light and tobacco smoke

Yates LR & Campbell PJ, Nat Rev Genetics, 2012
Classical DC Sense Molecular Clues to Mature, Migrate in dLNs and Present Tumor Ags to Activate Naïve T Cells
CD8 T Cell Responses Targeting Neoantigens are Central to Tumor Immunity
Factors Impacting Anti-Tumor Immunity

Factors Intrinsic to the Host

Factors Extrinsic to the Host

Adapted from Morad G et al., Cell, 2021
Factors Impacting Anti-Tumor Immunity

Factors Intrinsic to the Host

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Activated PD-1+ CTLs infiltrate the tumor core
Activated PD-1+ CTLs infiltrate the tumor core.

Evidence for TLS aggregates of immune cells with composition similar to lymph nodes.
Activated PD-1+ CTLs infiltrate the tumor core

Evidence for TLS aggregates of immune cells with composition similar to lymph nodes

CTLs are excluded from the tumor core

Binnewies M et al., Nat Med, 2018
Tumor microenvironment

Activated PD-1\(^+\) CTLs infiltrate the tumor core

Evidence for TLS aggregates of immune cells with composition similar to lymph nodes

CTLs are excluded from the tumor core

+ Immune desert tumors

Binnewies M et al., Nat Med, 2018
Tumor genotype and phenotype contribute to shape the TME

Cytokines/chemokines

Binnewies M et al., Nat Med, 2018
Tumor genotype and phenotype contribute to shape the TME

Cytokines/chemokines

Mutational landscape

Macrophages

GM-CSF

Reprogramming

p53 loss in tumor stroma has been shown to induce

Inflammatory macrophage

Immune regulatory macrophage

IL-1α

IL-1β

BRAF V600E

CMS1 tumor

Responsive to therapy

T_H1

High frequency of CD8+ T cells and T_H1

Double-strand breaks

CMS2, CMS3 and CMS4 tumors

High myeloid infiltrate

Low frequency of CD8+ T cells

Immunogenicity

Binnewies M et al., Nat Med, 2018
Defective Control by the Immune System Promotes Tumor Escape

- Genetic instability and tumour heterogeneity
- Immune selection
Tumor-Intrinsic Factors

Spranger S & Gajewski T, Ann Rev Immunol, 2018
Tumor-Intrinsic Factors

Loss of peptide-MHC-I expression

Peptide-MHC-I

Ag

IFN-γR

Spranger S & Gajewski T, Ann Rev Immunol, 2018
Tumor-Intrinsic Factors

Loss of peptide-MHC-I expression

Loss of antigen expression

Immunoediting

IFN-γR
Tumor-Intrinsic Factors

Immunoediting

Increased survival

Loss of peptide-MHC-I expression

Loss of antigen expression

Ablated signaling

IFN-γR

JAK

Spranger S & Gajewski T, Ann Rev Immunol, 2018
Tumor-Intrinsic Factors

Immunoediting

Increased survival

Immunoregulation

Loss of peptide-MHC-I expression

Loss of antigen expression

Ablated signaling

Chronic signaling

Increased expression of immune inhibitory factors (e.g., PD-L1, IDO)

Spranger S & Gajewski T, Ann Rev Immunol, 2018
T Cell Exhaustion: A Major Cause for Tumor Immune Escape

Binnewies M et al., Nat Med, 2018
T Cell Exhaustion: A Major Cause for Tumor Immune Escape

**T cell exhaustion**

T cell state characterized by:

1. High expression levels of inhibitory receptors
2. Loss of effector functions
3. Loss of proliferative capacity

Binnewies M et al., Nat Med, 2018
Establishment of an Immunosuppressive Environment
Establishment of an Immunosuppressive Environment

Both Innate and Adaptive Immune Cells Contribute to Create a Pro-Tumorigenic Milieu in the TME
Monocyte-Derived Myeloid Cells Accumulate in Tumors

Binnewies M et al., Nat Med, 2018
Monocyte-Derived Myeloid Cells Accumulate in Tumors

Antitumor CD8⁺ T cell activators cDC1 are progressively depleted from the tumor core

Binnewies M et al., Nat Med, 2018
Major Pro-Tumorigenic Functions Assumed by Macrophage Populations in Tumors

- Angiogenesis
- Metabolism
- Tissue remodelling and fibrosis
- Genetic instability
- Taming of adaptive immunity
- Regulation of tumour-promoting inflammatory cells
- Proliferation
- Epithelial-to-mesenchymal transition
- Cancer-stem-cell niche
- Invasion
- Metastasis
Dynamic Remodeling of Tumor and TME along Disease Evolution