Eterogeneità antigenica del tumore e immunoterapia

Antonio Curti

Department of Specialistico, Experimental and Diagnostic Medicine, Institute of Hematology “L. and A. Seràgnoli”, University of Bologna, Bologna, Italy
"Science's editors have chosen cancer immunotherapy as Breakthrough of the Year for 2013, a strategy that harnesses the body's immune system to combat tumors. It's an attractive idea, and researchers have struggled for decades to make it work".
Emerging Hallmarks of Cancer

- Deregulating cellular energetics
- Resisting cell death
- Inducing angiogenesis
- Genome instability and mutation
- Sustaining proliferative signaling
- Enabling replicative immortality
- Avoiding immune destruction
- Evading growth suppressors
- Activating invasion and metastasis
- Tumor-promoting Inflammation

Cell 2011 144, 646-674
Tumour antigens and T lymphocytes: “croce e delizia” for immunologists

Graphical representation of clonal evolution from the primary tumour to relapse in UPN 933124, and patterns of tumour evolution observed in eight primary tumour and relapse pairs.

Intratumor heterogeneity and clonal evolution: the immunological pressure

Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer.
Degree of mutational load and a specific neoepitope signature correlates with a clinical benefit from CTLA-4 blockade in melanoma patients.
Heterogeneity and prognostic value of neoantigen landscape in primary NSCLC

Neoantigen clonal architecture and clinical benefit of immune checkpoint blockade
Figure 1. A General Model of Hematopoiesis.
Specificity of immune responses against the malignant cancer-initiating cell depends on where antigen targets are expressed in the cell differentiation hierarchy.

The CML model as prototypical of hematopoietic stem-cell disorder where anti-leukemia immunological pressure may be curative, but where antigen-specific approaches have provided dismal results.
Harnessing the immune system to treat cancer
More TILs* Within a Tumor, Higher the Chances Immunotherapy Might Work Against It

* TILs = Tumor Infiltrating Lymphocytes

Highly versus Poorly infiltrated

- e.g. melanoma
- e.g. prostate cancer

Immune cell | Tumor cell

Can results be translated between them?

Mechanisms of Immune Escape may Differ:

- ↑ checkpoint inhibitory ligands
- ↑ T regs, IDO, immunosuppressive factors
- ↓ DC infiltration
- ↓ CD8 T cell infiltration
- ↑ Immunosuppressive oncogenic pathway signaling

Treg = Regulatory T cell
IDO = Indoleamine 2, 3-dioxygenase
DC = Dendritic cells

https://www.researchgate.net/profile/Alexandre_Reuben/publication/303599217_Monitoring_immune_responses_in_the_tumor_microenvironment/links/574e268608ae82d2c6be2a84.pdf
Examine the Tumor Microenvironment

- Determine the inhibitory pathways that are dominant
- Determine what agents to use in certain tumor types to release the inhibition
- Characterize tumors by
  - PD-L1 expression (high or low)
  - T-cell infiltrate (present or absent)
- Predictors of response by the presence of CD8+, CD4+, PD-1+, and PD-L1+ cell densities within the tumor and the invasive margin
- Logistic regression model indicates the best predictor for response in decreasing order:
  - CD8+ density in the invasive margin
  - CD8+ T-cell density in the tumor and invasive margin
  - PD-1+ and PD-L1+ density in tumor and invasive margin
  - CD4+ density in tumor and invasive margin was the worst predictor

B7 and CD28 family members deliver costimulatory and coinhibitory signals to T cells.

T cell Bim levels reflect responses to anti-PD-1 cancer therapy

Dronca RSU, JCI, 2016
Changes of Bim levels predict responses to anti–PD-1 therapy in melanoma patients

Dronca RSU, JCI, 2016
Upregulation of PD-L1/2 is responsible for the efficacy of the anti–PD-1 antibody pembrolizumab in primary mediastinal large B-cell and in Hodgkin lymphoma.

Fernando Cabanillas, and Noridza Rivera Blood 2017;130:234-235
Response to novel immunotherapy approaches: the role of tolerogenic pathways
Resistance to Blinatumomab

- High checkpoint inhibitors
- Loss of surface CD19
- Presence of Treg
- Intrinsic T cell defect due to chemo
- Extramedullar disease

No T cell activation and proliferation

No cytotoxicity
Loss of CD19 on the surface of leukemic blasts as a novel mechanism of leukemia escape, emerging during anti-CD19 targeting with new agents

CD19 loss demonstrates the potent selective pressure of novel immunological agents that drives extreme and specific escape strategies by leukemic blasts.

Patients with CD19-negative relapsed leukemia have very poor prognosis and novel approaches to treat and ideally prevent antigen-loss are direly needed.

1) Immunological «toxicity» is coupled with efficacy
2) Limits of antigen-driven immunological approach
PD-L1 induction in ALL blasts correlates with resistance to Blinatumomab
Induction of PD-1 and CTLA-4 on T cells during attack of malignant lymphoblast cells mediated by Blinatumomab.
Treg number correlates with response in R/R ALL patients treated with blinatumomab (N=42)

Table 2. Analysis of potential prediction markers

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<th>Non-responder</th>
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<th>P-value</th>
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Abbreviations: AlloTx, allogeneic stem cell transplantation; LDH, lactate dehydrogenase.
Studio del repertorio immunologico del paziente

Selezione dei pazienti su base «immunologica»

Studio del microambiente immunologico e non

Studio della popolazione blastica
IMMUNOSENESCENCE

**B lymphocyte**
- Reduced development and numbers of naïve B cells
- Decreased diversity of B cell repertoires and B cell responses to new antigens

**T lymphocyte**
- Reduced development and numbers of naïve CD4^+^/CD8^+^ T cells
- Decline in CD4^+^ function and in CD8^+^ T cell cytotoxicity + proliferation
- Reduced generation of Th subsets

**NK cell**
- Reduced cytolytic potential and CD1 expression in NKT cells
- Decreased cytokine and chemokine production

**Neutrophils**
- Decreased phagocytosis, chemotaxis and apoptosis function

**Macrophage**
- Defective phagocytosis
- Decreased cytokine production, antigen presentation and superoxide anion production

**Dendritic cell**
- Reduced IFN production and expression of CD25 and ICAM-1 in mature MODCs
- Reduction in lymphocyte cytotoxicity and greater migratory capacity of monocyte-macrophage derived APCs
“One of the striking findings that distinguishes cancer patient responders from non-responders after PD-1 blockade immunotherapy is the ratio of putatively favorable to unfavorable bacteria.”

Laurence Zitvogel et al. Science 2018;359:1366-1370
The Gut Microbiota in Response and Toxicity to Immunotherapy

Gopalakrishnan V, Cancer Cell, April 2018
1) **Identification of immunological biomarkers predictive of response to immunotherapy approaches**

- deep characterization of T-cell repertoire (change viewpoint: from a tumor-cell based to an immune cell-based standpoint)
- the role of tolerogenic cells (and pathways)
- integrating tumor cell genetic instability and mutational landscape with the effect of immunological pressure (immunoediting model)

2) **Integrating intratumoral clonal heterogeneity with sensitivity to immune response**

- the question of neo-antigens (private versus generalized)
- how to target stem cell compartment (mechanisms of immunological resistance)

3) **Elucidating novel (and old) mechanisms of immune escape of tumor cells to new agents**
Immunogenomics and cancer immunotherapy

- **Immunogenic**
  - Checkpoint blockade
  - Immune agonists
  - Vaccines
  - TCR transgenics

- **Immunologically inert**
  - Targeted therapy
  - CAR T therapy
  - Bi-specific Abs
  - MoAbs / ADC

- **Biomarkers to assess tumor intrinsic and tumor extrinsic factors that affect antitumor immunity**

- **Combination based on other biomarkers such as Tregs, TAMs, mutations, etc**
Cancer immunoediting: Equilibrium

Deepak Mittal et al, Current Opinion in Immunology, Volume 27, 2014, 16 - 25
“If it is possible to protect small laboratory animals in an easy and safe way against infectious and highly aggressive neoplasms, then it will be possible to do the same for human patients.”

Paul Ehrlich, 1897