Immunity and Therapeutic Efficacy

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Disclosures

• Advisory Boards/Consulting: IMV, Symvivo, Virogin, Akamara
• Contracted Research: Zymeworks
• Co-Founder, CEO: Innovakine Therapeutics
Tumor-infiltrating lymphocytes (TIL) in human cancer

Ovarian cancer

CD8+ killer T cells
CD4+ T cells
CD20+ B cells
Tumor cells

Milne et al, unpublished
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3 requirements:
• Antigens
• Access
• Activity
Three major TIL patterns in cancer

Three cases of ovarian cancer:

- **Cold**
  - Few TIL

- **Warm**
  - Weak TIL
  - T cells in stroma

- **Hot**
  - Robust TIL
  - T cells and B cells in epithelium & stroma

CD4+ T cells
CD8+ T cells
CD20+ B cells
Three major TIL patterns in cancer

Three cases of ovarian cancer:

Cold
Few TIL

Warm
Weak TIL
T cells in stroma

Hot
Robust TIL
T cells and B cells in epithelium & stroma

→ favorable prognosis
Patients often present with a mixture of hot, warm and/or cold tumors.

Allen Zhang, Rob Holt, Sohrab Shah, et al. Cell 2018
Hypothesis: do TIL patterns represent a temporal sequence?

**Ovarian cancer:**

- **Cold**
- **Hot**
- **Warm**

**Cells:**
- CD4+ T cells
- CD8+ T cells
- CD20+ B cells
Tumor evolution gives rise to intratumoral heterogeneity

Clonal Theory (Nowell 1976)

- Founder cell
- Normal/Healthy Cell
- Tumor Population 1
- Tumor Population 2
- Tumor Population 3
- Clonal Mutation (exist in all cancer cells)
- Subclonal Mutations (exist in a subset of cancer cells)
Tumor evolution gives rise to intratumoral heterogeneity

Somatic mutations provide an “arrow of time” for tumor evolution
Tumor evolution leads to intratumoral heterogeneity

Clonal phylogeny in ovarian cancer (patient 4)
TIL are negatively associated with intratumoral heterogeneity

Polyclonal tumors tend to be cold
Monoclonal tumors tend to be hot

Clonal phylogeny in ovarian cancer (patient 4)

Allen Zhang, Rob Holt, Sohrab Shah, et al. Cell 2018
Hot tumors show signs of immune editing

- **e.g. Patient 15**

**HLA allelic loss:**

- Loss of: HLA–A*24:02
- Loss of: HLA–B*13:01
- Loss of: HLA–C*03:04

**Neoantigen depletion:**

- Observed/expected subclonal neoantigen rate

Allen Zhang, Rob Holt, Sohrab Shah, et al. Cell 2018
Lung cancer: immune evasion is linked to prognosis

- Non-small-cell lung cancer: 88 cases and 258 specimens
- Hot tumors show decreased clonal diversity and increased immune editing (neoantigen and/or HLA loss)
- The extent of immune evasion was key to prognosis

Rosenthal R…Swanton C. Nature 2019
How does the immune response change over time and treatment?

Clonal Theory (Nowell 1976)

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Time
Immune cell composition in the TME changes dramatically during cancer progression

Lung squamous cell carcinoma
77 cases, 122 biopsies, 9 stages

Mascaux C...Galon J, Nature 2019
Chemotherapy can enhance TIL density

Neoadjuvant chemotherapy of ovarian cancer

CD3 CD8 TIA-1

Pre Post

CD8+ TIL:


Similar effects reported for hormone, radiation and targeted therapies in other cancers
Checkpoint blockade can select for a variety of immune evasion mechanisms.
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Number of cases showing a given resistance mechanism:

- **B2M**: n=9
- **Other**: n=10
- **JAK**: n=3
- **Neoantigen depletion**: n=4
- **WNT**: n=2
- **PTEN**: n=6
- **VISTA**: n=8
- **LAG3**: n=5
- **TIM3**: n=5
- **Unknown**: n=19

Schoenfeld AJ and Hellmann MD, Cancer Cell 2020
Despite their prognostic benefit, hot tumors can exhibit:

- Antigen loss
- MHC loss
- High proportion of bystander T cells
- Multiple immune suppressive factors
  - *PD-1, TIGIT, LAG3, CD39, Tregs etc.*
- Loss of tumor-reactive T cells over time
Tumor-infiltrating T cells exhibit major limitations

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*How do TIL promote patient survival???
Tumor-infiltrating T cells, B cells & macrophages co-aggregate in tumors

- T cells (CD3)
- B cells/plasma cells (CD79a)
- Macrophages (CD68)
- PD-L1
Tumor-infiltrating T cells and B cells show a combined effect on survival

Article

B cells are associated with survival and immunotherapy response in sarcoma


Article

Tertiary lymphoid structures improve immunotherapy and survival in melanoma


Article

B cells and tertiary lymphoid structures promote immunotherapy response

Optimal TIL responses involve both cytolytic and antibody-based mechanisms.
Optimal TIL responses involve both cytolytic and antibody-based mechanisms.
Take home messages

• Tumor microenvironment is a complex ecosystem with multiple effector & regulatory cell types & factors
  • Ecological principles apply
• Tumors evolve under numerous selective pressures, including the immune response
  • Evolutionary principles apply
• Our challenge is to devise therapeutic strategies that force the extinction of tumor cells while sparing host tissues
  • Today’s immunotherapies are achieving this in some patients and inspiring the next generation of strategies!