NKG2A checkpoint receptor expression on tumor-infiltrating CD8+ T cells restrains efficacy of immunotherapy
I have the following financial relationships to disclose:

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I will not discuss off label use and/or investigational use in my presentation.
HLA-E is generally overexpressed in cancer

Healthy tissue

Cancer tissue

Ovary

A

C

89%

Strong HLA-E expression:
- Colorectal
- Lung
- Gastric
- Melanoma
- Vulva
- HNSCC
- Breast
- Ovarium
- .....  

Cervix

E

G

85%

Low HLA-E

High HLA-E

The NKG2A --- HLA-E axis in cancer

In homeostasis:
- HLA-E is a conserved, non-classical HLA molecule
-Expressed in immune privileged tissues
-Low expression in healthy tissues
-Engaged by inhibiting receptor NKG2A
-NKG2A is only expressed on killers: NK and killer T cells

In cancer:
-Overexpression of HLA-E correlates with worse prognosis
-Neutralizes beneficial effect of T cell infiltrate

T van Hall
NKG2A as a checkpoint inhibitor on CD8 T cells
26-Apr-17
NKG2A expression on human TIL

% CD8 T cells of TIL

% NKG2A+ of CD8+

Gooden et al, PNAS 2011

HNSCC: IR = ex vivo immune response
Co-inhibitors on human TIL: unique populations

Co-expression of PD-1 and NKG2A

Flow analysis of TIL (HNSCC)

Do not post

NK subsets
CD8 T subsets

Mass cytometry analysis of TIL

T van Hall
NKG2A as a checkpoint inhibitor on CD8 T cells

26-Apr-17
Co-expression of inhibitory receptors on mouse TIL
(Mouse model 1: TC-1 in C57BL/6 mice)

CD8 T cells in TIL

naive

vaccinated

TC-1 model

Do not post
Therapeutic vaccination increases NKG2A and Qa-1 (Mouse model 1: TC-1 in C57BL/6 mice)

- Influx of immune cells
- NKG2A+ TIL
- Enhanced Qa-1 expression on tumor

Also found in B16 model
Enhanced efficacy of vaccination in absence of Qa-1 (Mouse model 1: Qa-1 knockdown TC-1 in C57BL/6 mice)

Similar T cell induction

Stronger vaccination efficacy

WT TC-1 tumor

Qa-1\(^{ko}\) TC-1 tumor

TC-1 model
NKG2A blocking mAb recapitulates genetic model (Mouse model 1: TC-1 in C57BL/6 mice)

Tumor vaccine NKG2A mAb

day: 0 8 18 22 29

Percent survival

no treatment
NKG2A mAb
vaccine + control mAb
vaccine + PD-1 mAb
vaccine + NKG2A mAb

Tumor size (mm³)

Days

no treatment
Vaccination + control mAb
Vaccination + NKG2A mAb

Days

TC-1 model
NKG2A expression and blockade therapy with PD-1 (Mouse model 2: A20 in BALB/c mice)

NKG2A expression on TIL

- NK cells: 62% NK cells, 36.5% CD8+ T cells
- CD8+ T cells: 12% NK2A+, 81% CD8+

....on CD8 T cells after PD-1 therapy

- CD8+ lymphocytes (%): 0.5

Combination therapy

- Control
- anti-NKG2A mAb
- anti-PD-1 mAb
- anti-NKG2A + anti-PD-1 mAbs

Survival (%)

- Days
- Spleen
- Tumor
Conclusions

- NKG2A checkpoint receptor:
  - is expressed on intratumoral NK (~60%) and CD8 T cells (~15%)
  - enhanced frequencies after PD-1 blockade therapy and after vaccination

- The ligand HLA-E (=Qa-1 in mice):
  - is generally overexpressed in cancer
  - is upregulated after vaccination

- The NKG2A-HLA-E axis may confer adaptive resistance to immunotherapy
- Combo treatment with NKG2A and PD-1 blockade, or with vaccination is powerful
People involved

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