Tumor-intrinsic $\beta$-catenin signaling mediates tumor-immune avoidance
CD8⁺ T cell-inflamed melanoma shows signs of increased immune suppressive mechanisms

Spranger, STM 2013
Anti-PD-1 therapy appears to be preferentially effective in T cell-inflamed tumors

Tumeh, Nature 2014
What causes the non-T cell-inflamed tumor phenotype?
Workflow to identify oncogenic pathways differentially activated between T cell-inflamed and non-T cell-inflamed patients
49% of non-T cell-inflamed tumors were linked with active $\beta$-catenin signaling.
Experimental model system

Tamoxifen
Genetically engineered mouse tumors with active β-catenin lack T cell infiltration

IF on tumor

Flow cytometry

Red: T cells  
Blue: nuclei
Is the lack of T cell infiltration caused by a lack of initial T cell priming?

Braf$^{V600E/PTEN^{-/-}}$
Braf$^{V600E/PTEN^{-/-}/CAT-STA}$

+/- LoxP-Stop-LoxP SIY
β-catenin-expressing tumors fail to prime 2C TCR Tg T cells
β-catenin-expressing tumors show reduced numbers of CD8α+ and CD103+ dendritic cells
Which signal is required for CD103+ dendritic cells to infiltrate into the tumor?
CCL4 expression is lost in $\beta$-catenin$^+$ tumors
Knockdown of ATF3 restores CCL4 expression in $\beta$-catenin$^+$ tumor cells

$BP$ cell line from $Braf^{V600E}/PTEN^{-/-}$; $BPC$ cell line from $Braf^{V600E}/PTEN^{-/-}/CAT-STA$
Does $\beta$-catenin-mediated lack of T cell infiltration facilitate resistance towards checkpoint inhibition?
Checkpoint blockade fails to control β-catenin-expressing tumors

Combination therapy of αCTLA-4 and αPD-L1

Analysis of tumor growth and T cell infiltration

![Graphs showing tumor growth with and without combination therapy](image_url)
Tumor-intrinsic $\beta$-catenin signaling mediates lack of T cell infiltration and resistance towards checkpoint inhibition

Spranger et al., Nature 2015
Does tumor-intrinsic $\beta$-catenin signaling mediate resistance to an existing immune response?
Experimental approach to evaluate impact of tumor-intrinsic $\beta$-catenin on effector/memory T cell efficacy
Existing antigen-specific T cell memory fails to control \( \beta \)-catenin\(^+ \) tumors expressing the shared antigen

\( \beta \)-catenin wild type \hspace{1cm} \beta \)-catenin activated \hspace{1cm} Antigen-negative
Is the lack of effector T cell recruitment due to a lack of memory re-activation?

Or in addition due to a lack of recruitment of effector T cells into the tumor microenvironment?
BPC-SIY tumor fail to recruit \textit{in vitro} activated antigen-specific 2C T cells
β-catenin-expressing SIY<sup>+</sup> tumors fail to recruit primed antigen-specific 2C T cells
Adoptive transfer of effector 2C T cells fails to control β-catenin-expressing tumors.
Which cell type within the tumor microenvironment is required for effective effector T cell recruitment?
CD103+ dendritic cells are the predominant source of CXCR3 chemokine ligands
Are dendritic cells within the tumor microenvironment sufficient for the recruitment of effector T cells?
Reconstitution of BPC-SIY tumors with FLT3-L derived DC restored the capability of tumors to recruit T cells.
Reconstitution of $\beta$-catenin-expressing SIY$^+$ tumors with FLT3L-DCs restores effector T cell recruitment
Tumor cell-intrinsic $\beta$-catenin mediates immune exclusion against pre-existing antigen-specific T cell memory.
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Injection of Flt-3L BMDCs can “reverse” the non-inflamed phenotype

- 17 days
- Twice per week
- Analysis of T cell and DC infiltration

Flt-3L DC activated with poly(I:C)
Effector T cells isolated from BP tumors express high levels of CXCR3
Increased tumor control is accompanied by increased peripheral and intra-tumoral immune response

Response to secondary tumor
Increased tumor control is accompanied by increased peripheral and intra-tumoral immune response.

Response to secondary tumor