Cross-dressed dendritic cells drive anti-tumor immunity

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Metabolic Adaptations Establish Immunotherapy Resistance in Melanoma

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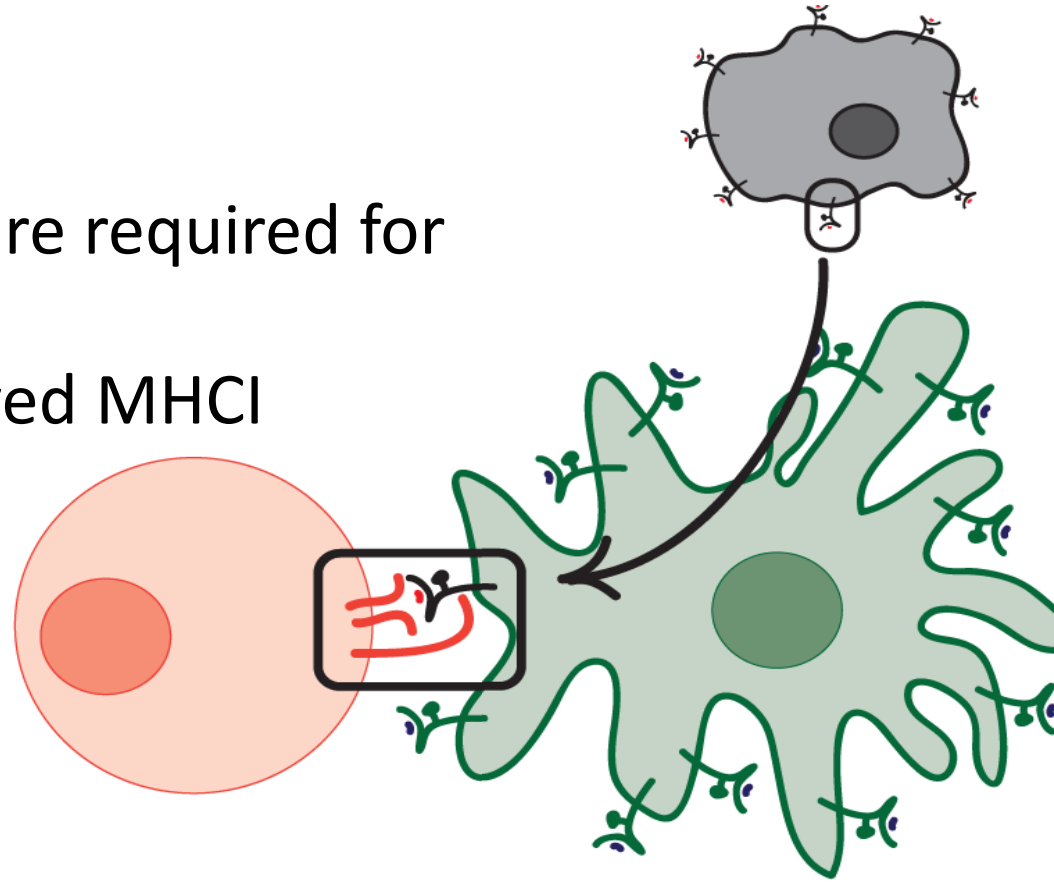
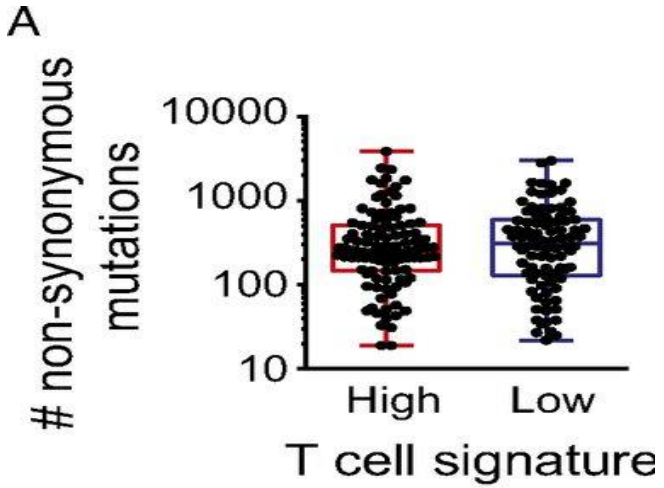
Is a defect in T cell priming an underlying cause of “cold tumors”?

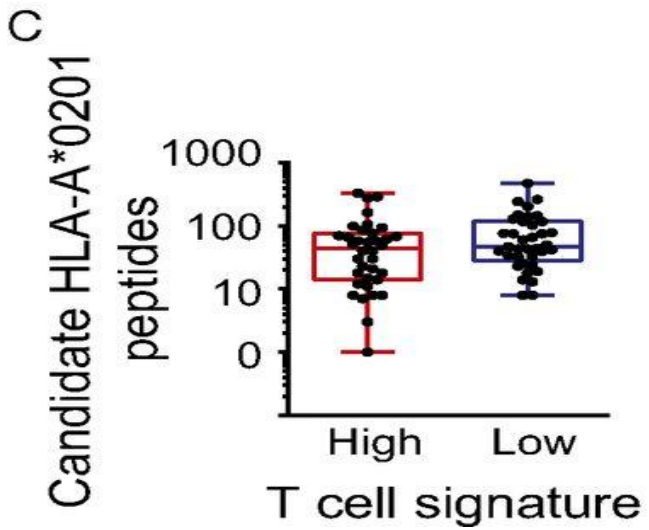
Cross-Dressing Dendritic Cells

- BATF3-lineage DCs and tumor-derived MHCI are required for tumor-specific $CD8^+$ T cell priming.
- Tumor resident APCs acquire cancer cell-derived MHCI molecules.



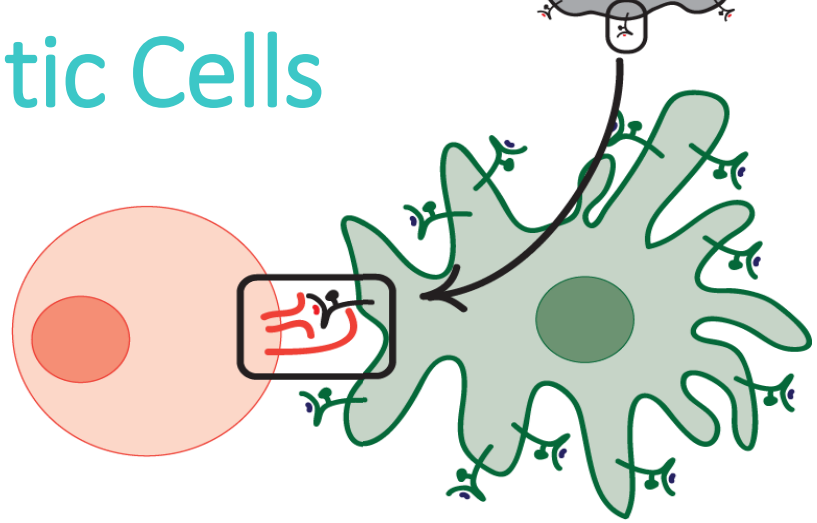
Density of immunogenic antigens does not explain the presence or absence of the T-cell–inflamed tumor microenvironment in melanoma





Stefani Spranger et al. PNAS 2016;113:E7759-E7768

Cross-Dressing Dendritic Cells



Questions??

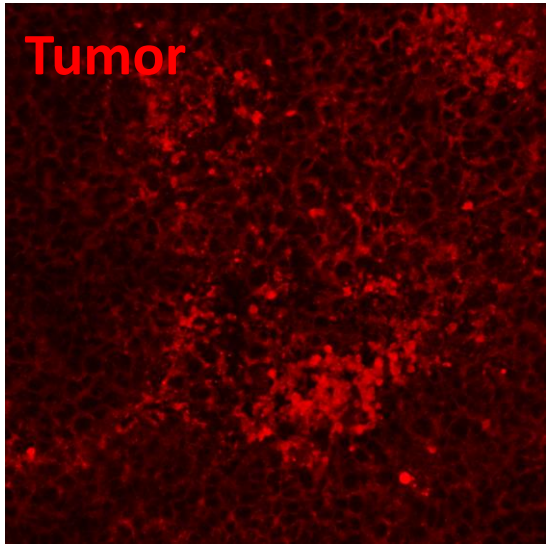
1. **How are the MHC complexes acquired?** Phagocytosis? Exosomes?
2. **Do the Tumor cells have to die for MHC spread?** What types of death will increase cross-dressing?
3. **Is cross-dressing going to be more prevalent than cross presentation?** If so, what are differences in the pathways?
4. **What types of therapies/treatments will enhance cross-dressing?**

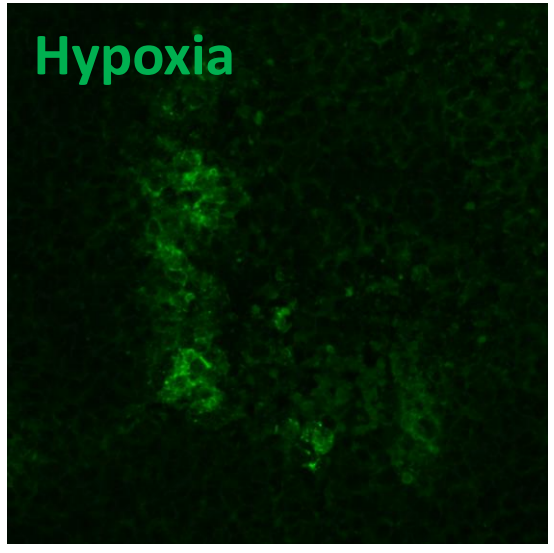
Metabolism Matters!!

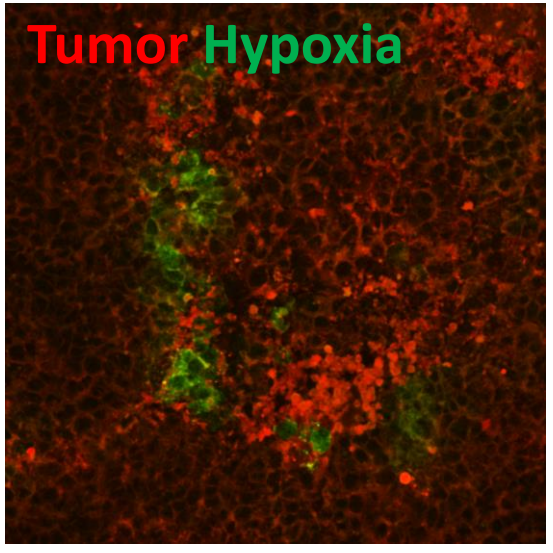
Resistant Tumor Cells Adapted to Survive in Hypoxic Tumor: Treatment

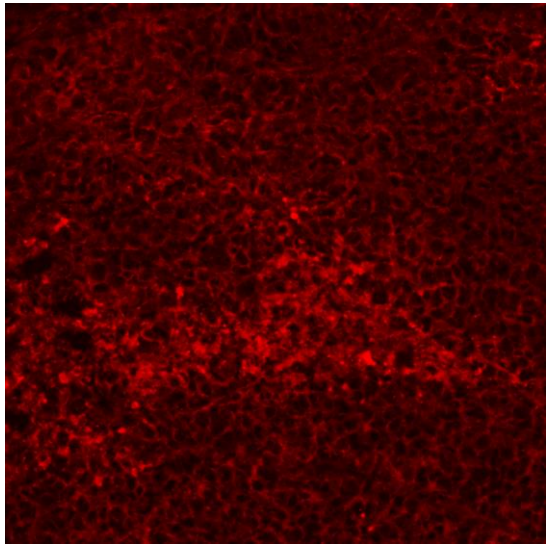
Parental Tumor

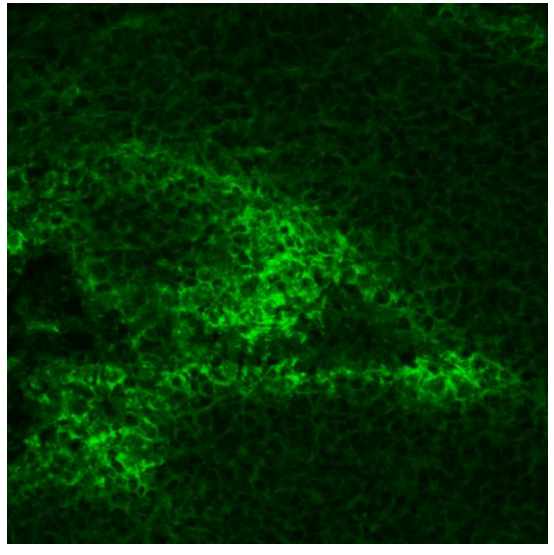
Resistant Tumor

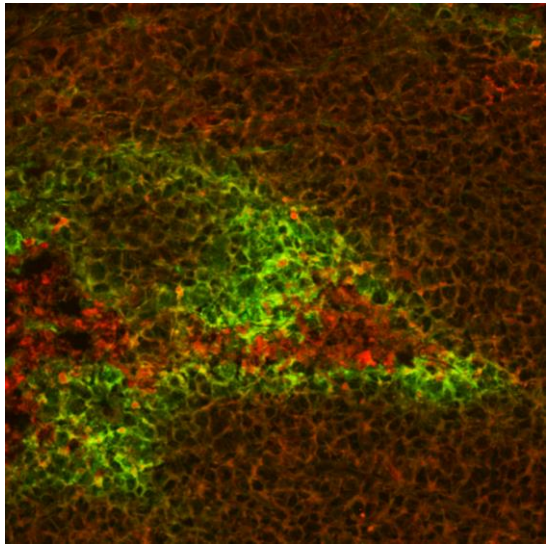








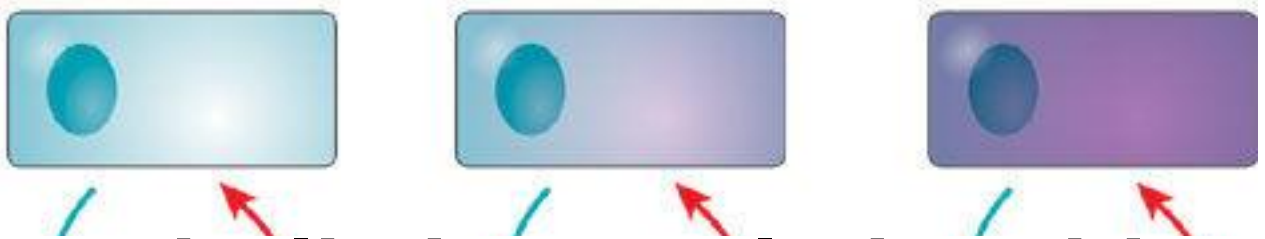




Immunotherapy
FVAX
αCTLA-4
αPD-1
αPD-L1

Heterogeneous & Dynamic Metabolic states

Tumor Cells



Metabolic inter-relationships

TILs

metabolic state
function
phenotype

Glycolysis
OXPHOS

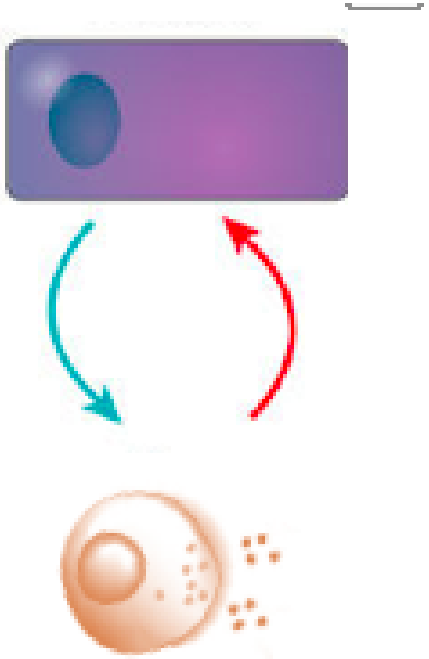
“Warburg effect”

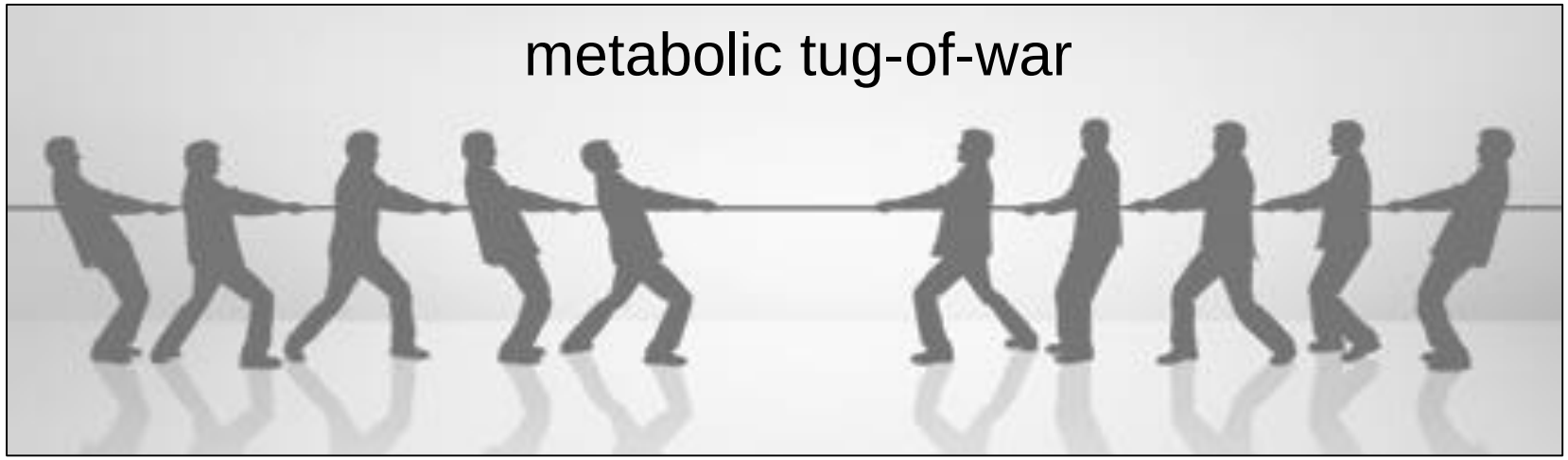
Lactate
Increase acidity
Decrease in glucose availability
Increased PD-L1
Hypoxia

Weiyi Peng/Patrick Hwu
Greg Delgoff/ McLane Watson
Ping-Chih Ho

****patients with high LDH levels are more resistant to immunotherapy**

Do the TILs adapt to metabolic alterations induced by the tumor cells?





Does the anti-tumor immune response select for more metabolically-aggressive tumors that then evades anti-tumor immunity?

How can we measure the metabolic states of cancer cells? How is this related to immuno-evasive states (PD-L1,

How does this vary across the tumor spatially and in different metastatic sites? Is the metabolic state of the tumor influenced by tissue of origin or site metastasis?

Can we identify “sweet spots” that cripple cancer cell growth, but not anti-tumor immunity? (inhibitors of Ldha, Mct1, GLS (glutaminase)).