



CHOP Expression Regulates MDSC Accumulation and Function in Tumors

Paul Thevenot, PhD

Presidential Session

SITC 29th Annual Meeting

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Presenter Disclosure Information

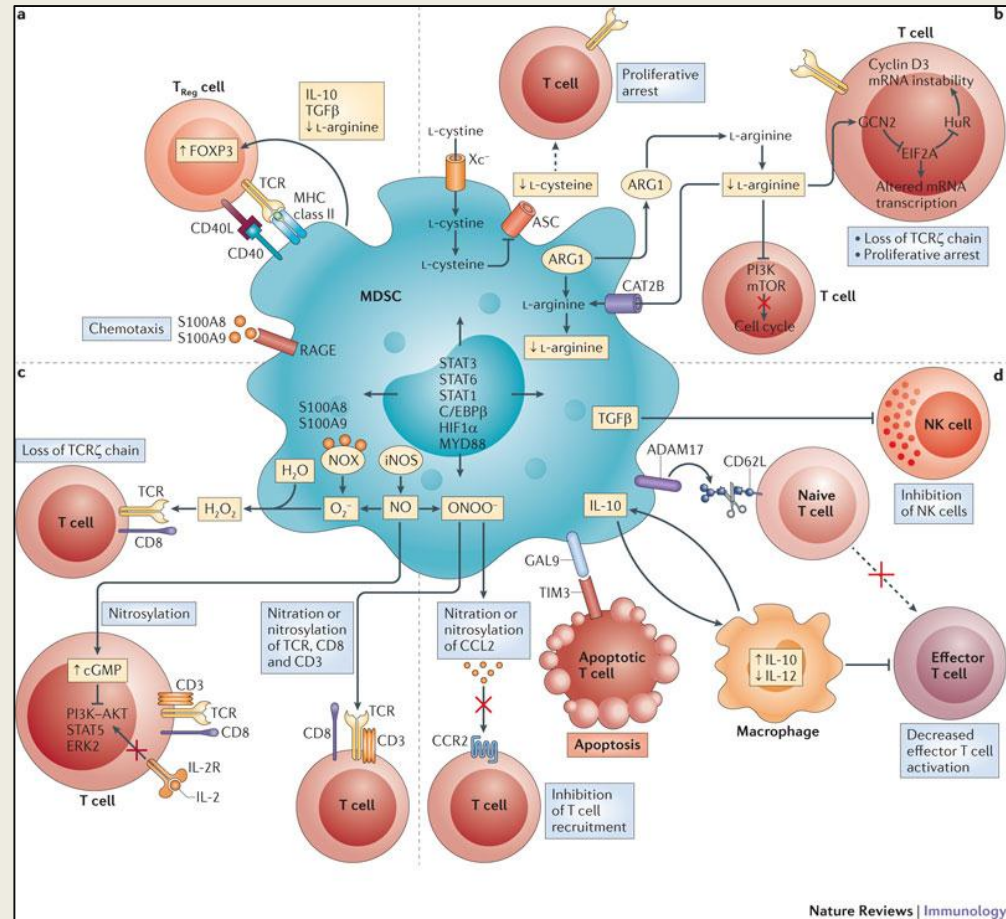
Paul Thevenot, PhD

The following relationships exist related to this presentation:

No Relationships to Disclose

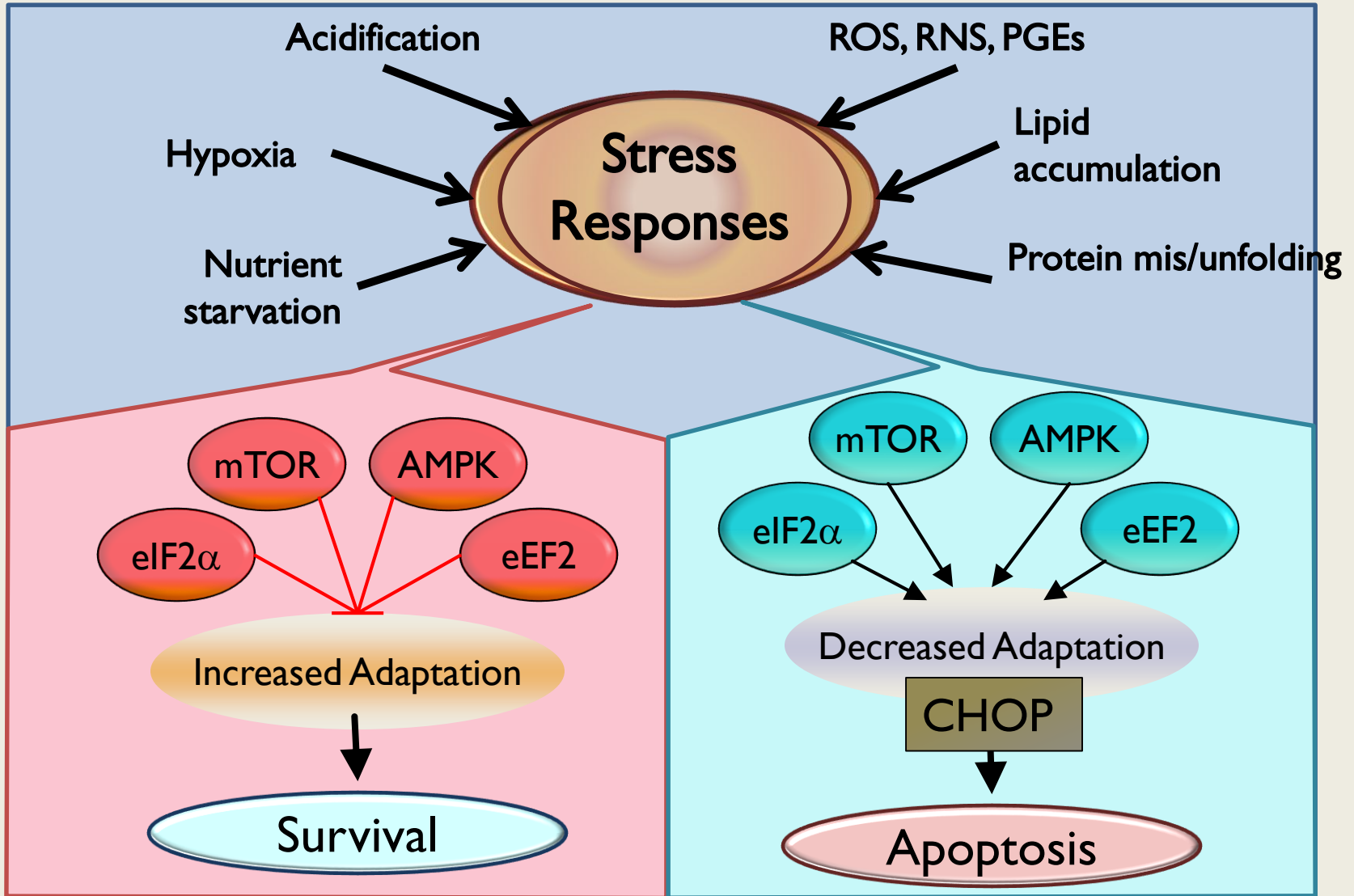
Myeloid-derived Suppressor Cells (MDSCs)

- Role of immune dysfunction in cancer persistence and progression
- Accumulate in pathological inflammatory conditions.
- Tolerogenic and immune suppressive activity.
- Several mechanisms of suppression.
- Limited therapies to block MDSC function.



Gabrilovich et al. 2012, Nature Reviews Immunology

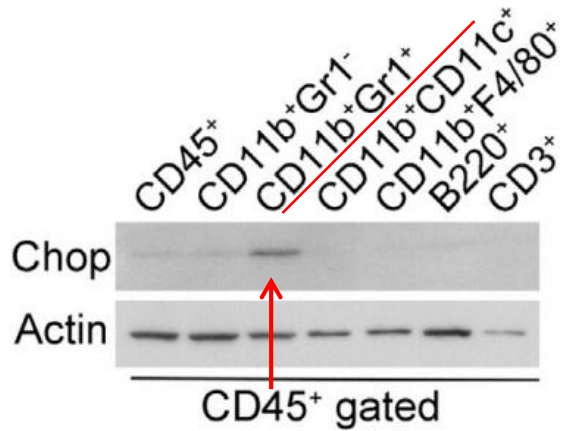
Response to Tumor-derived Stress Factors



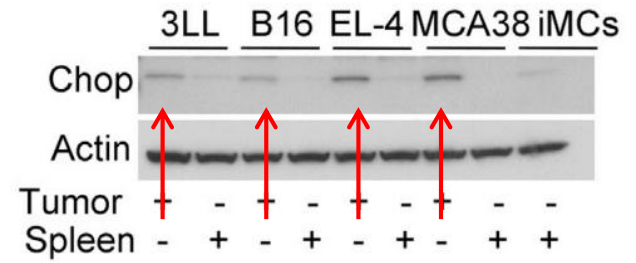
Gap of knowledge. The interaction between tumor-linked stress and anti-tumor immunity remains practically unknown.

CHOP Expression in Tumor-Infiltrating MDSCs

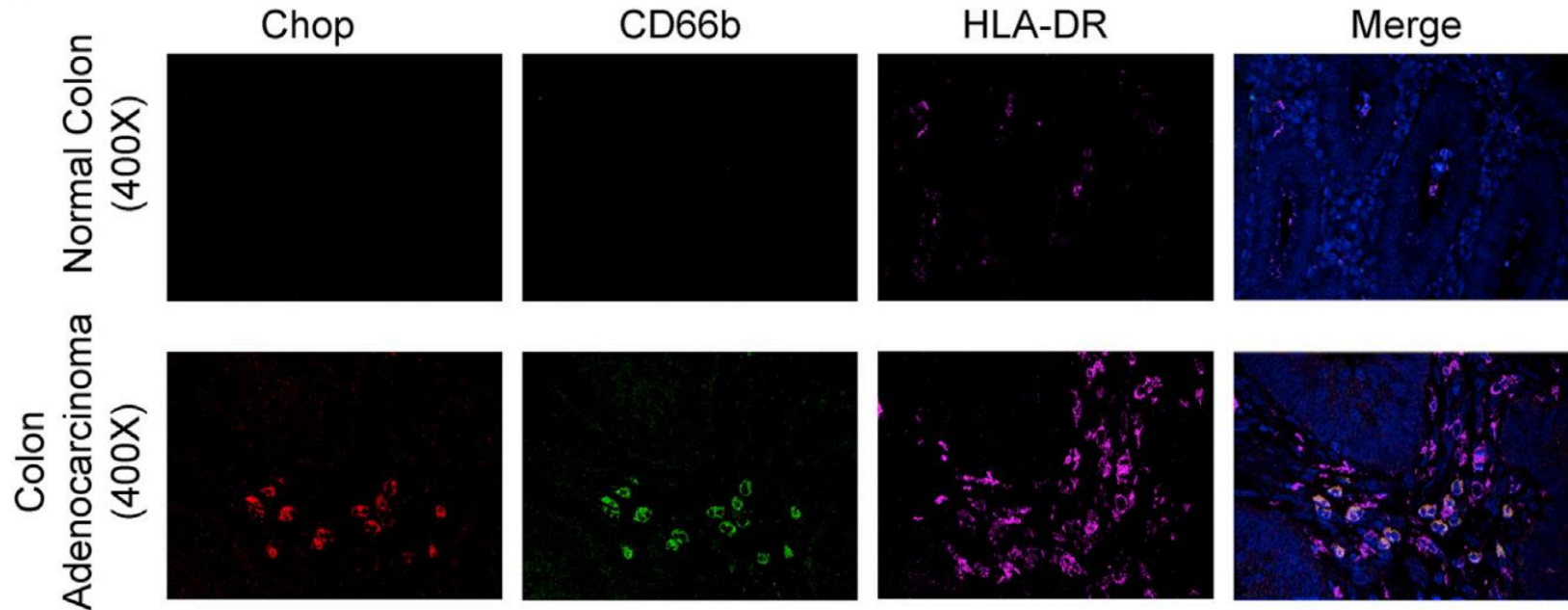
CHOP Expression in CD45⁺CD11b⁺Gr1⁺ MDSCs



CHOP Elevated in Tumor MDSCs

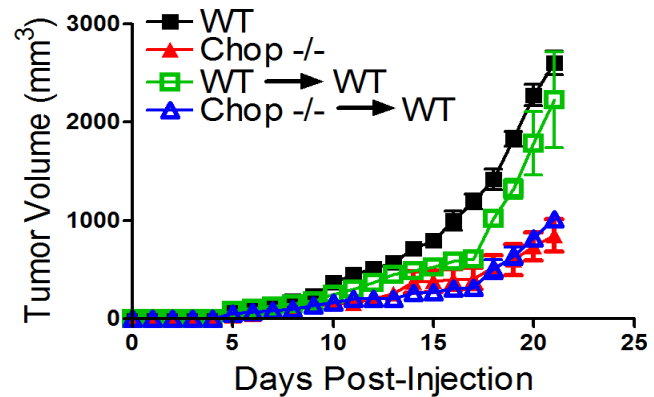
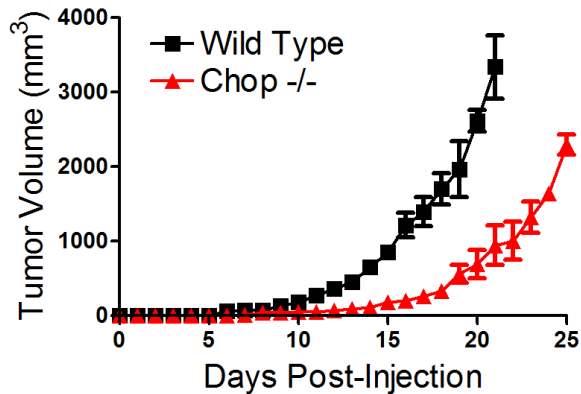


CHOP Expression in Human Tumor-Infiltrating MDSCs

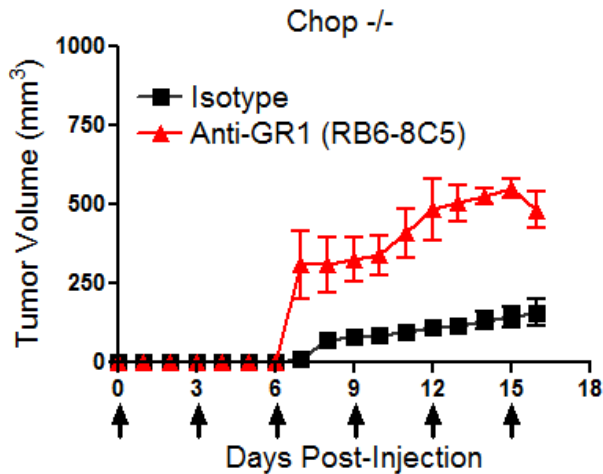


Deletion of CHOP in MDSCs Delays Tumor Growth

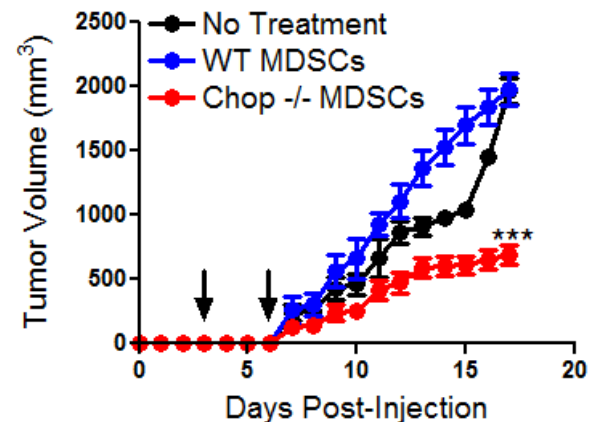
Delayed Tumor Growth in CHOP $-/-$ and Chimeric CHOP $-/-$ Mice



MDSC Partially Restores Tumor Growth

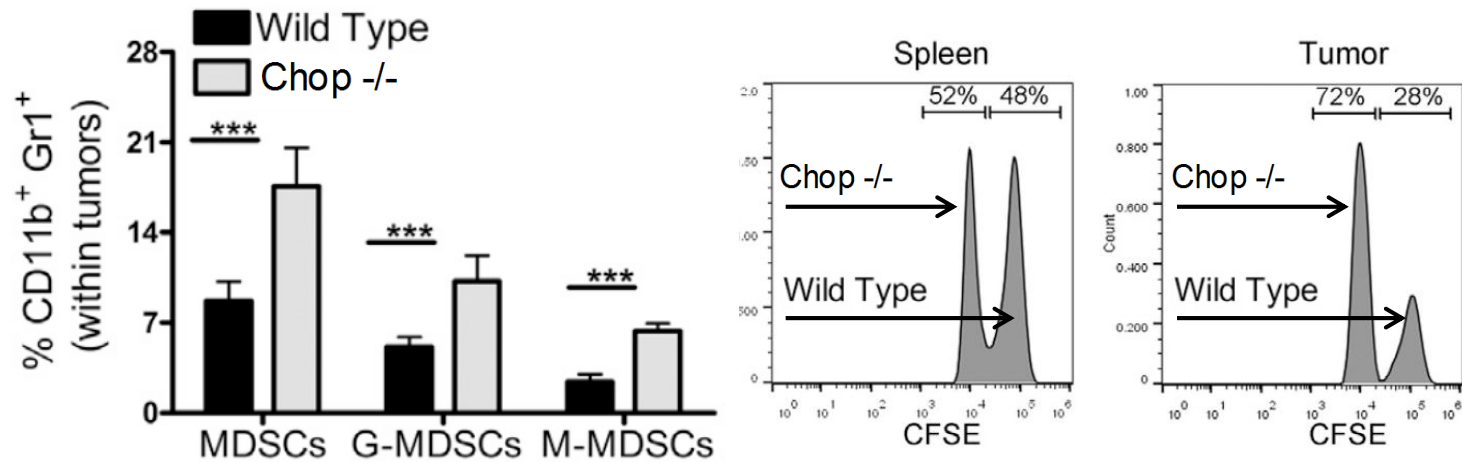


Therapeutic Effect of CHOP $-/-$ MDSCs

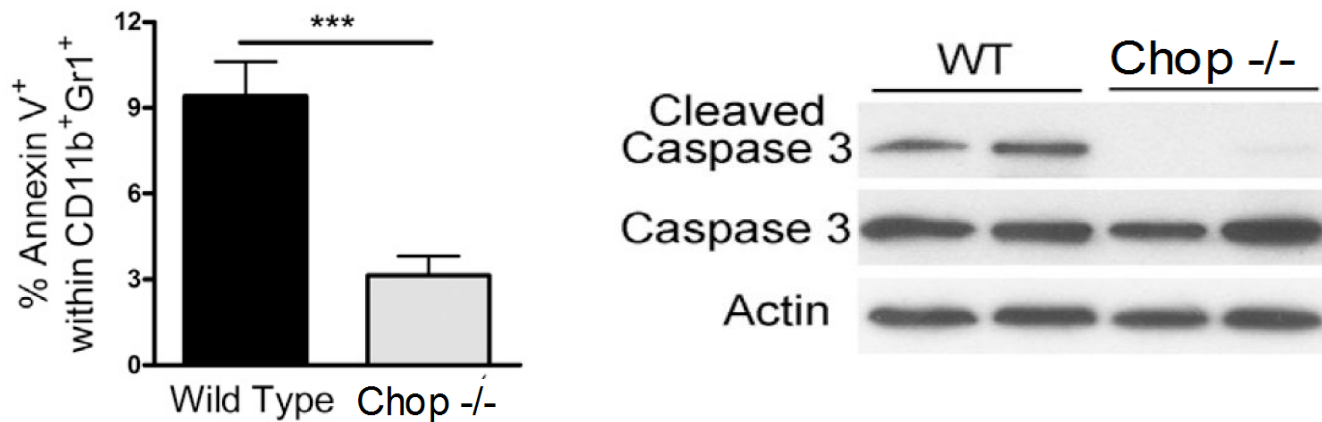


Role of CHOP in MDSC Accumulation and Turnover

Increased Accumulation of CHOP $-/-$ MDSCs at the Tumor Site

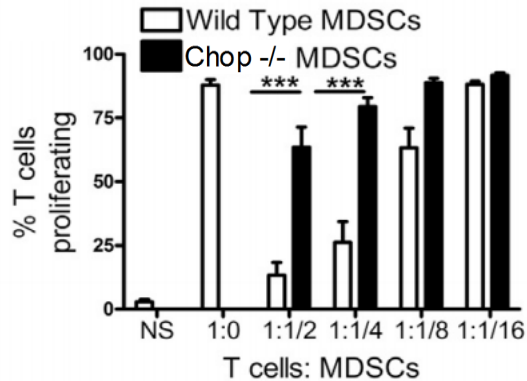


Decreased Turnover of CHOP $-/-$ MDSCs

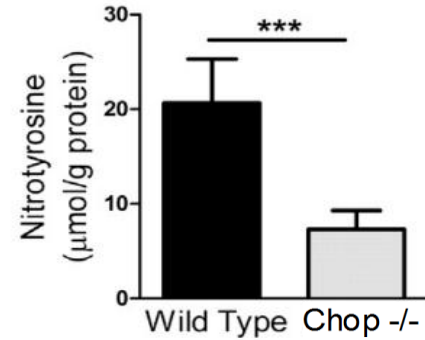
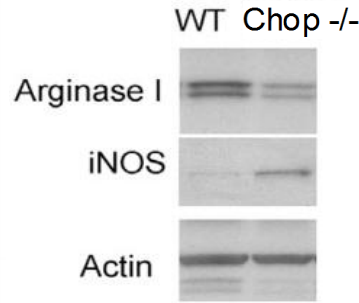


Chop Deletion Alters MDSC Function

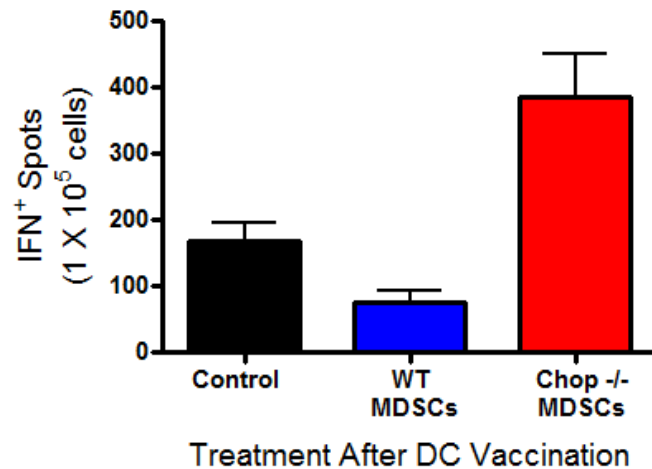
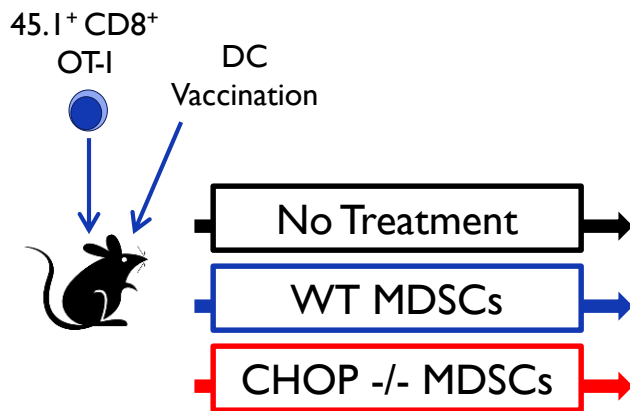
Decreased Suppressive Activity



Decreased Arginase I and PNT Production



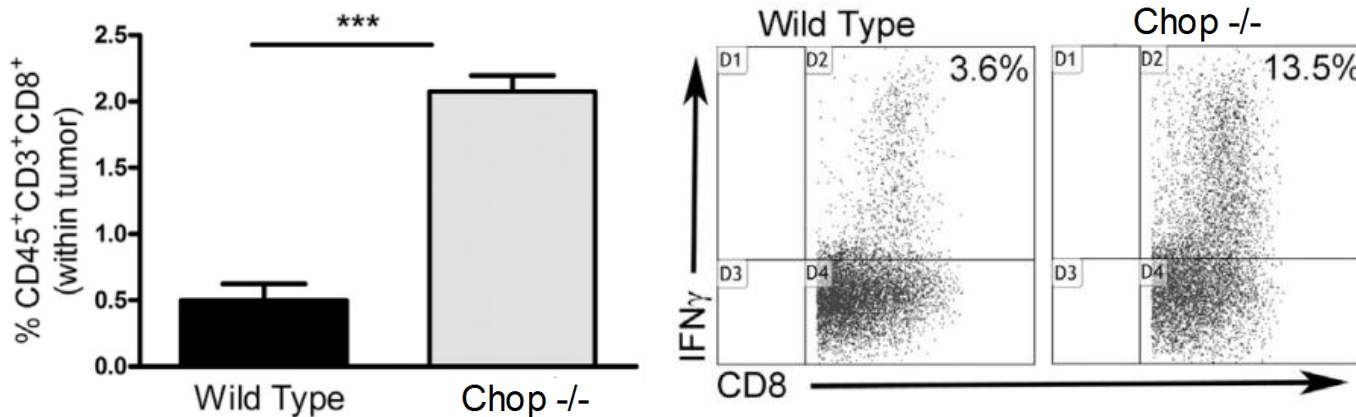
In Vivo Tolerogenic Effect of MDSC Transfer Reversed by Chop Deletion



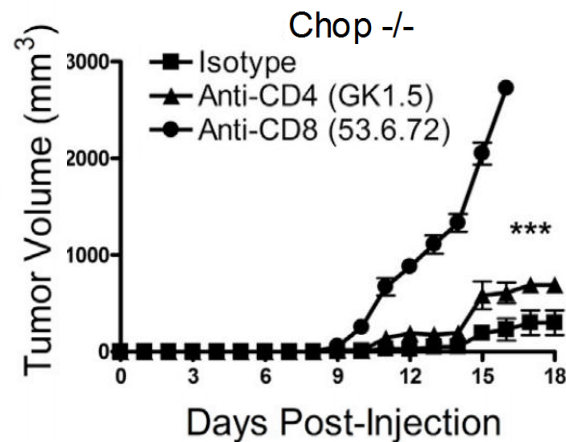
CHOP Deletion in MDSCs Overcomes Induced T Cell Dysfunction

Tumor

Increased Tumor CD8⁺ T-cell Accumulation and IFN γ Production

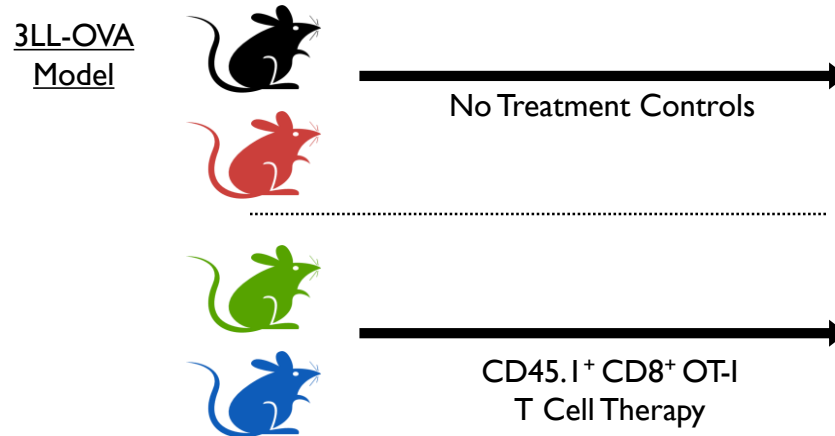


CD8⁺ Depletion Restore Tumor Growth in CHOP -/-

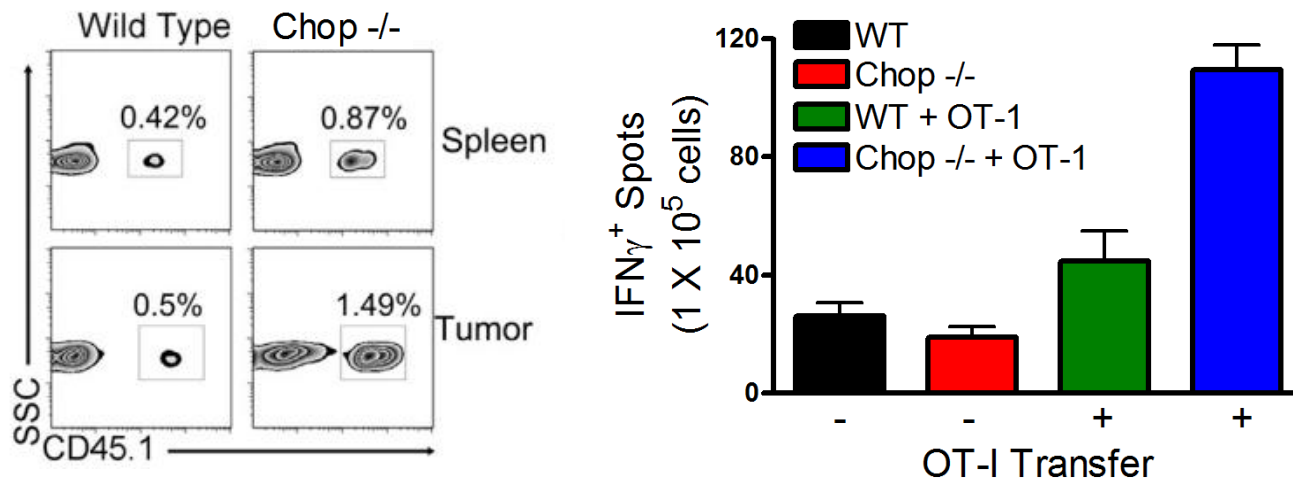


CHOP Deletion in MDSCs Overcomes Tumor-Induced Tolerance

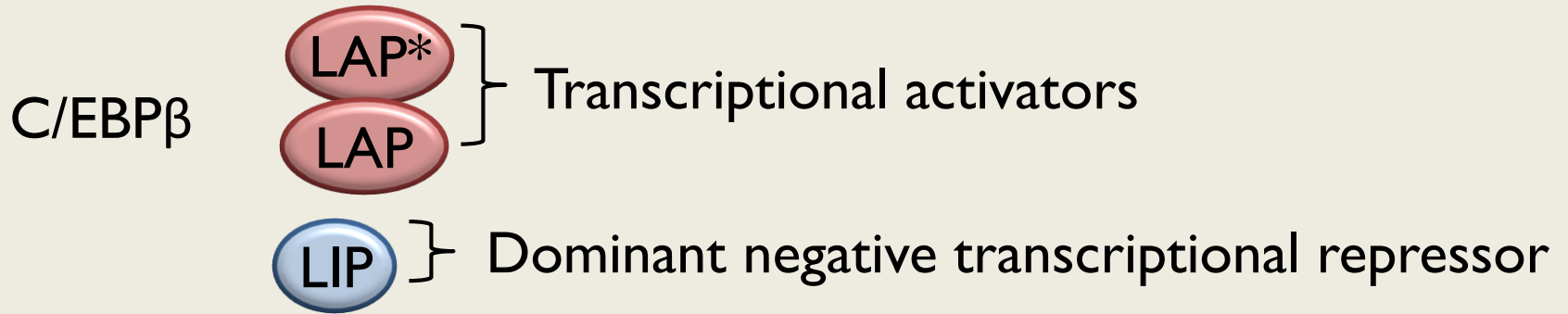
MDSC Tolerance Against Tumor Antigen-Specific T Cell Immunotherapy



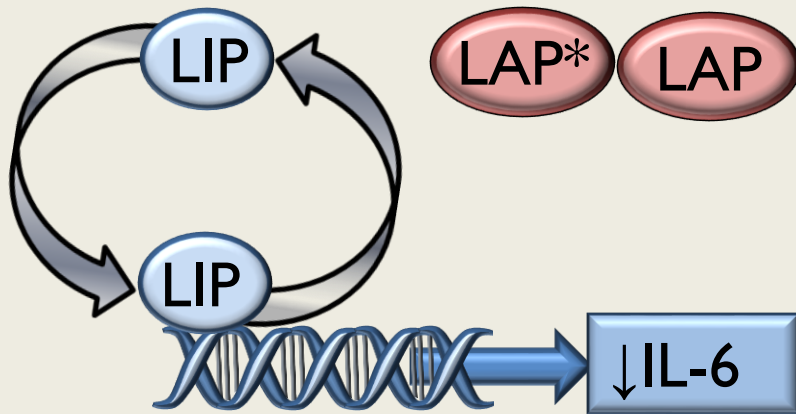
Increased Antigen-specific CD8⁺ T-cell Accumulation and IFN γ Production in CHOP -/-



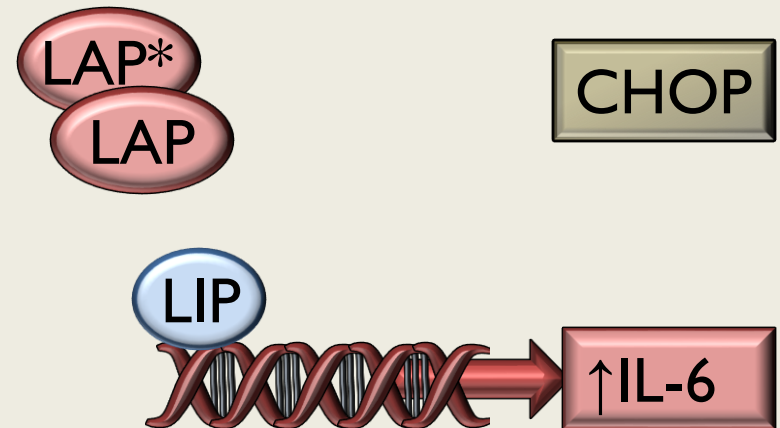
Pro-inflammatory Function of CHOP in Promoting C/EBP β Activity



Homeostasis

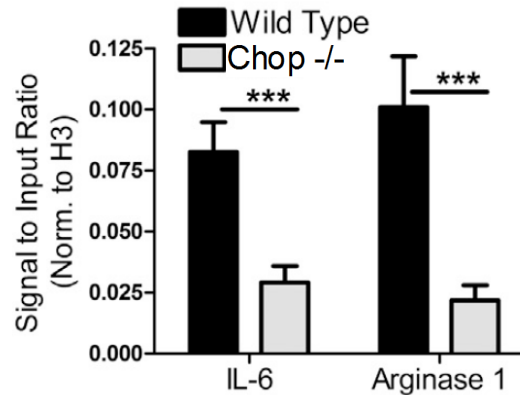
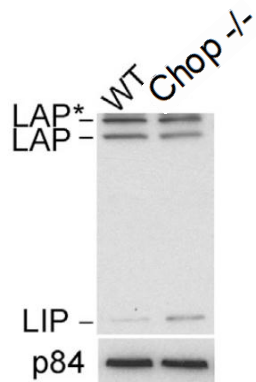


Stress Responses

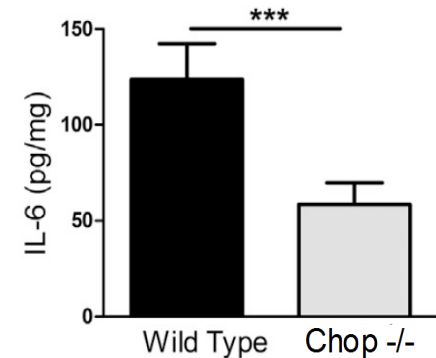


CHOP Activates MDSC Suppression Through Modulating C/EBP β Activity and IL-6 Production

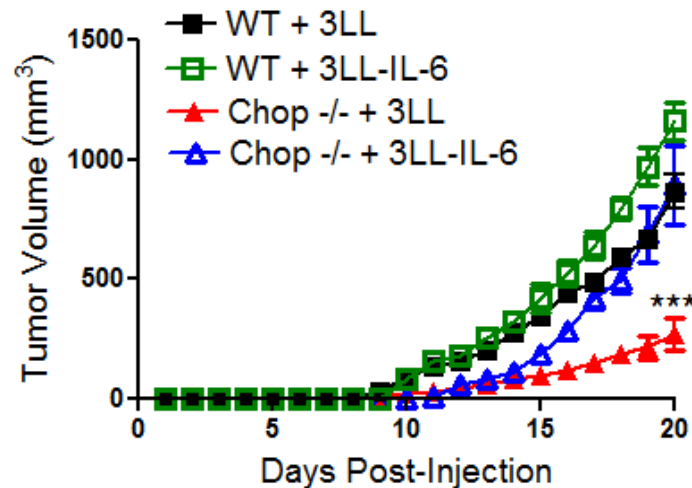
Increased LIP Levels and Decreased C/EBP β Activity in CHOP $-/-$ MDSCs



Decreased IL-6 in CHOP $-/-$ MDSCs



Protective Effect of CHOP $-/-$ Reversed by Overexpressing IL-6



Conclusions

- Tumor-derived factors lead to Chop expression in MDSCs
- Chop deletion alters MDSC function and suppressive activity
- The protective effect of Chop deletion in MDSCs is mediated by increase accumulation and anti-tumor activity of CD8⁺ T cells
- CHOP deletion impairs C/EBP β activity reducing production of MDSC suppressive mediators IL-6 and Arg I
- Chop represents an attractive target to specifically target MDSC suppressive activity in solid tumors

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