CHOP Expression Regulates MDSC Accumulation and Function in Tumors

Paul Thevenot, PhD

Presidential Session

SITC 29th Annual Meeting
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
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

Normal Colon (400X)

Colon Adenocarcinoma (400X)
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

<table>
<thead>
<tr>
<th></th>
<th>Wild Type</th>
<th>Chop -/-</th>
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<tbody>
<tr>
<td>MDSCs</td>
<td></td>
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<td>G-MDSCs</td>
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<td>M-MDSCs</td>
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Decreased Turnover of CHOP -/- MDSCs

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<tr>
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<th>Wild Type</th>
<th>Chop -/-</th>
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<tbody>
<tr>
<td>Cleaved Caspase 3</td>
<td></td>
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<tr>
<td>Caspase 3</td>
<td></td>
<td></td>
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<tr>
<td>Actin</td>
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Chop Deletion Alters MDSC Function

<table>
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<tr>
<th>Decreased Suppressive Activity</th>
<th>Decreased Arginase I and PNT Production</th>
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<tr>
<td>Wild Type MDSCs</td>
<td>Nitrotyrosine (μmol/g protein)</td>
</tr>
<tr>
<td>Chop -/- MDSCs</td>
<td><strong>Wild Type</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Chop -/-</strong></td>
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<tr>
<td>% T cells proliferating</td>
<td><em>WT</em></td>
</tr>
<tr>
<td>T cells: MDSCs</td>
<td><strong>Chop -/-</strong></td>
</tr>
<tr>
<td>NS</td>
<td>***</td>
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<tr>
<td>1:0</td>
<td>***</td>
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<td>1:1/2</td>
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<td>1:1/4</td>
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<td>1:1/16</td>
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In Vivo Tolerogenic Effect of MDSC Transfer Reversed by Chop Deletion

45.1^CD8^ OT-I DC Vaccination

- No Treatment
- WT MDSCs
- CHOP -/- MDSCs

IFN^+ Spots (1 X 10^5 cells)

Control
WT MDSCs
Chop -/- MDSCs

Treatment After DC Vaccination
CHOP Deletion in MDSCs Overcomes Tumor Induced T Cell Dysfunction

Increased Tumor CD8$^+$ T-cell Accumulation and IFN$\gamma$ Production

CD8$^+$ Depletion Restore Tumor Growth in CHOP -/-

Tumor Growth Study

- Isotype
- Anti-CD4 (GK1.5)
- Anti-CD8 (53.6.72)

Days Post-Injection

Tumor Volume (mm$^3$)
CHOP Deletion in MDSCs Overcomes Tumor-Induced Tolerance

MDSC Tolerance Against Tumor Antigen-Specific T Cell Immunotherapy

3LL-OVA Model

No Treatment Controls

CD45.1^+ CD8^+ OT-I T Cell Therapy

Increased Antigen-specific CD8^+ T-cell Accumulation and IFNγ Production in CHOP -/-
Pro-inflammatory Function of CHOP in Promoting C/EBPβ Activity

C/EBPβ
- LAP*
- LAP
- LIP

Transcriptional activators

Dominant negative transcriptional repressor

Homeostasis

Stress Responses

↓ IL-6

↑ IL-6

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

Increased LIP Levels and Decreased C/EBPβ 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/EBPβ 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
Acknowledgements

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