FAM46C-Dependent Tuning of Endoplasmic Reticulum Capacity in Multiple Myeloma

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No COI to declare
FAM46C belongs to a metazoan-specific family of proteins with 4 human members (A-D) sharing ~60% sequence identity but different tissue expression.

FAM46C is frequently and uniquely deleted/mutated in 20% myeloma patients, implying a PC-specific tumor suppressor activity.

(FAM46C/TENT5C in Multiple Myeloma)

(Barbieri et al., British Journal of Haematology, 2016)

(Bolli et al., Leukemia, 2018)
FAM46C reduces myeloma proliferation rate and increases apoptotic rate

FAM46C is a **MM-specific** tumor suppressor

**Silencing in WT MM line**

**Over-Expression in FAM46C-mutated MM lines**

**Non-MM cells**

Zhu et al.; Cancer Research 2017
Fucci et al., Cell Reports 2020
Manfrini et al., Cancer Research 2020
FAM46C stabilizes Ig and ER-targeted mRNAs

FAM46C is a non-canonical poly(a) polymerase that polyadenylates Ig mRNAs and other transcripts encoding ER-targeted proteins.

Mroczek et al.; Nat Commun 2017

Fucci et al.; Cell Reports 2020
**FAM46C boosts the secretory apparatus**

FAM46C Silencing in WT RPMI 8266

FAM46C Over-expression in OPM2 mut cells

**SILAC proteomic**

**Electron Microscopy**
FAM46C promotes Ig production and secretion

**OVER-EXPRESSION**

<table>
<thead>
<tr>
<th>RPMI 8266</th>
<th>Mock</th>
<th>shFAM46C</th>
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<tbody>
<tr>
<td>FAM46C</td>
<td>![Image]</td>
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<tr>
<td>Intracellular Lambda chain</td>
<td>![Image]</td>
<td>![Image]</td>
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<td>Secreted Lambda chain</td>
<td>![Image]</td>
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<tr>
<td>Actin</td>
<td>![Image]</td>
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**SILENCING**

<table>
<thead>
<tr>
<th>OPM2</th>
<th>Mock</th>
<th>FLAG-FAM46C</th>
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<tbody>
<tr>
<td>FAM46C</td>
<td>![Image]</td>
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FAM46C is induced under PRDM1 during plasma cell differentiation and sustains antibody production in vivo.

FAM46C potent induction upon plasma cell differentiation suggests a key role in the ER reshaping to sustain antibody secretion.
FAM46C interacts with FNDC3 proteins at the ER membrane

FAM46C interactome

<table>
<thead>
<tr>
<th>Protein</th>
<th>Control IP</th>
<th>FAM46C IP</th>
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<tbody>
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<td>FAM46C</td>
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<td>CTU2</td>
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</tbody>
</table>

FAM46C interacts with the ER transmembrane proteins FNDC3A and FNDC3B

Fucci et al.; Cell Reports 2020
FNDC3 proteins are required for FAM46C localization and activity

**mRNA stability**

**ER protein levels**

**ER localization**

_Fucci et al.; Cell Reports 2020_
FAM46 members differ in their effects on ER

FAM46C and FAM46D have the most potent effects on the ER
FAM46C and FAM46D boost secretion beyond sustainability

**Living cells (%)**

- Mock
- F46A
- F46B
- F46C
- F46D

**Days post infection**

![Graph showing living cells (%) over days post infection.]

**ROS levels**

- Mock
- F46A
- F46B
- F46C
- F46D

**OMF2**

![Graph showing ROS levels over CM-H2DCFDA.]

**ATP levels**

- Mock
- F46A
- F46B
- F46C
- F46D (FLAG-Tag)

![Graph showing ATP levels over days post infection.]

**Flag**

![Image showing Flag and Actin levels.]

**Actin**
FAM46C is tightly regulated by degradative pathways

1) FAM46C is rapidly degraded by the Ubiquitin Proteasome System (UPS)

2) UPS inhibition induces sequestration of FAM46C away from the ER in p62-positive aggregates
Conclusions

- FAM46C boosts the secretory capacity and Ig production through the interaction with the ER membrane proteins FNDC3A and FNDC3B.

- To ensure sustainability, FAM46C is rapidly degraded by the UPS or sequestered away from the ER in p62-positive aggregates.

- Basis for MM-specific oncosuppressive activity of FAM46C.

Fucci et al.; Cell Reports 2020
Immunity vs Malignancy

In MM patients **Loss of Function** mutations have been identified in PRDM1, XBP1 and FAM46C

Is MM trying to **reduce but not eliminate** Ig production?

Can we learn a lesson from MM genetics and understand how to modulate the secretory activity?
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