FAM46C-Dependent Tuning of Endoplasmic Reticulum Capacity in Multiple Myeloma

Enrico Milan

18th International Myeloma Workshop 2021

September 10th, 2021

Vienna, Austria

OSPEDALE SAN RAFFAELE

UNIVERSITÀ VITA-SALUTE SAN RAFFAELE
UniSR
QUID EST HOMO?

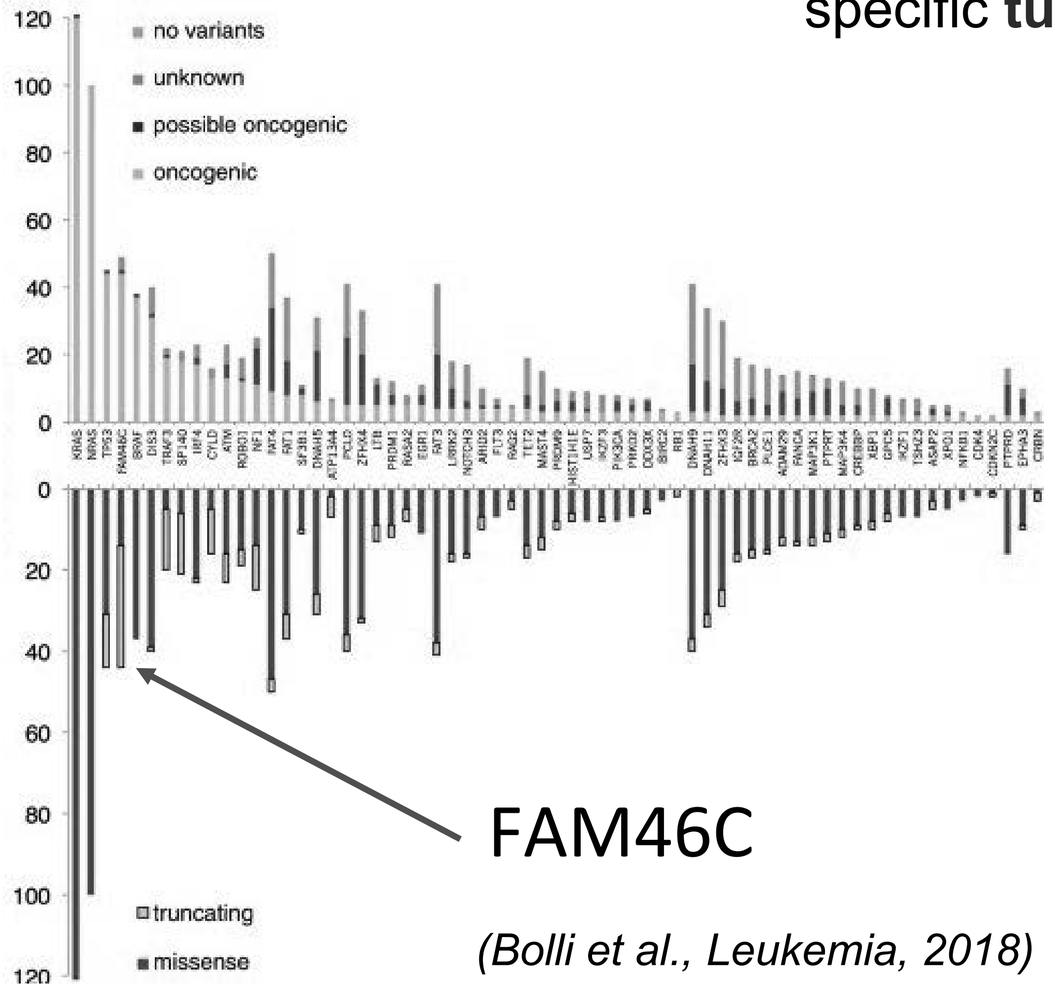
COI Disclosure

No COI to declare

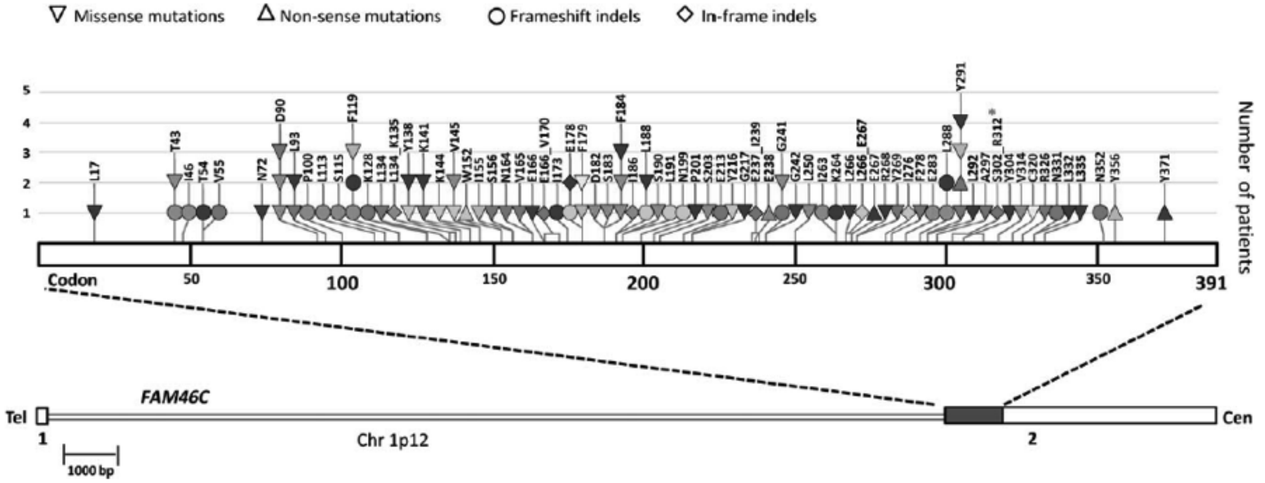
FAM46C/TENT5C in Multiple Myeloma

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.

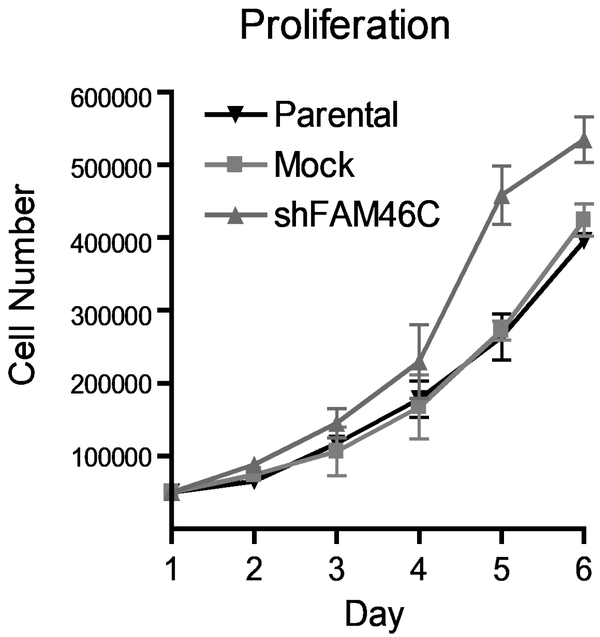


(Bolli et al., Leukemia, 2018)

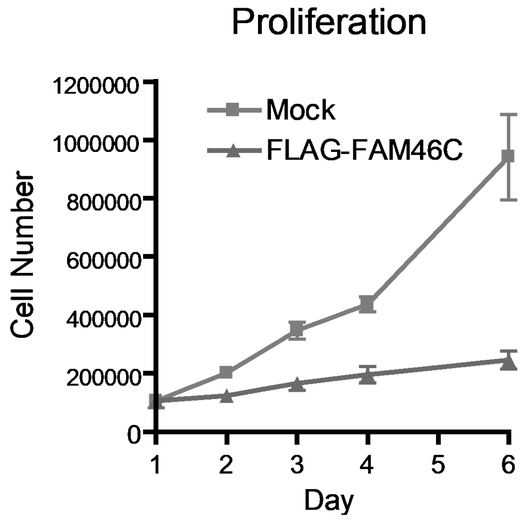


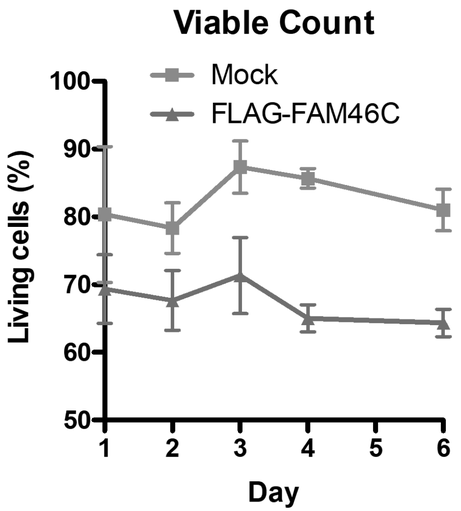
(Barbieri et al., British Journal of Haematology, 2016)

FAM46C reduces myeloma proliferation rate and increases apoptotic rate

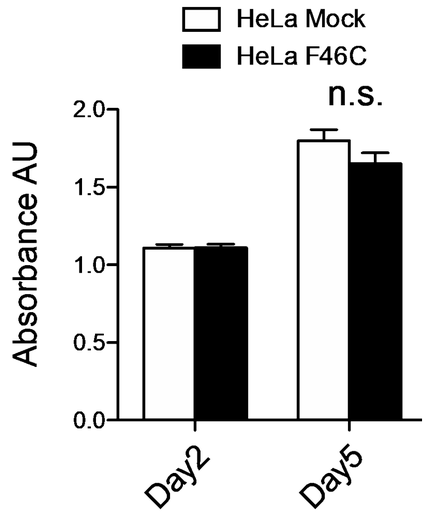


Silencing in WT MM line





Over-Expression in FAM46C-mutated MM lines

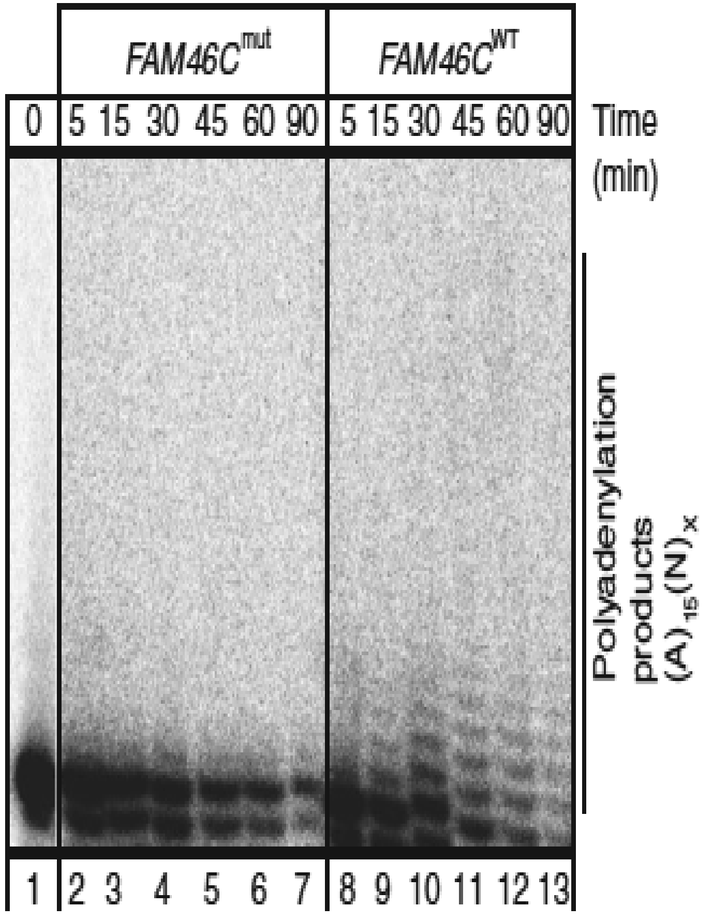


Non-MM cells

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

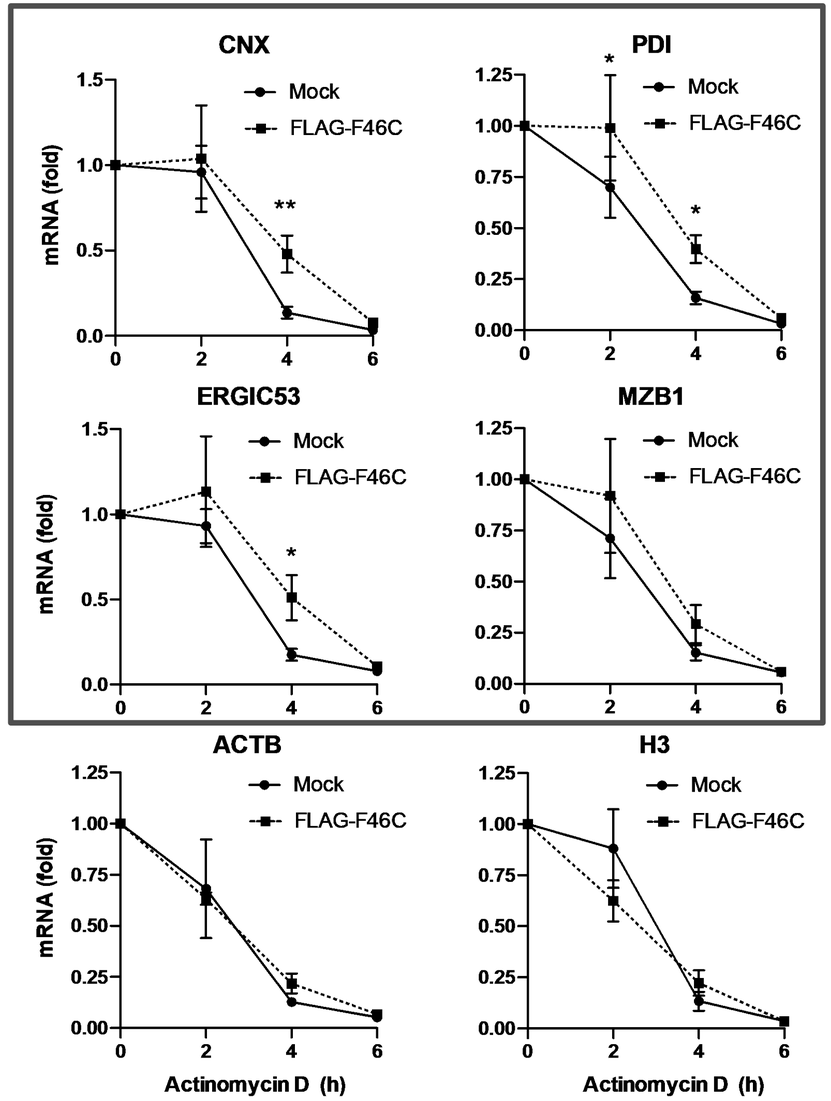
Zhu et al.; Cancer Research 2017
Fucci et al., Cell Reports 2020
Manfrini et al., Cancer Research 2020

FAM46C stabilizes Ig and ER-targeted mRNAs



Mroczek et al.; Nat Commun 2017

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

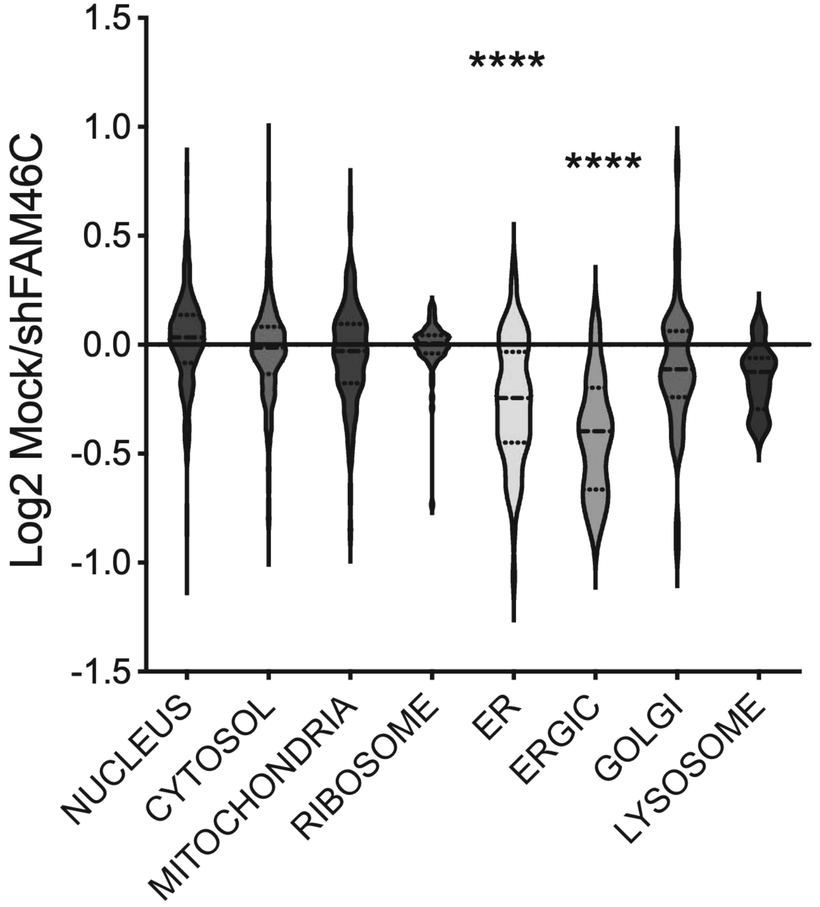


ER

Fucci et al.; Cell Reports 2020

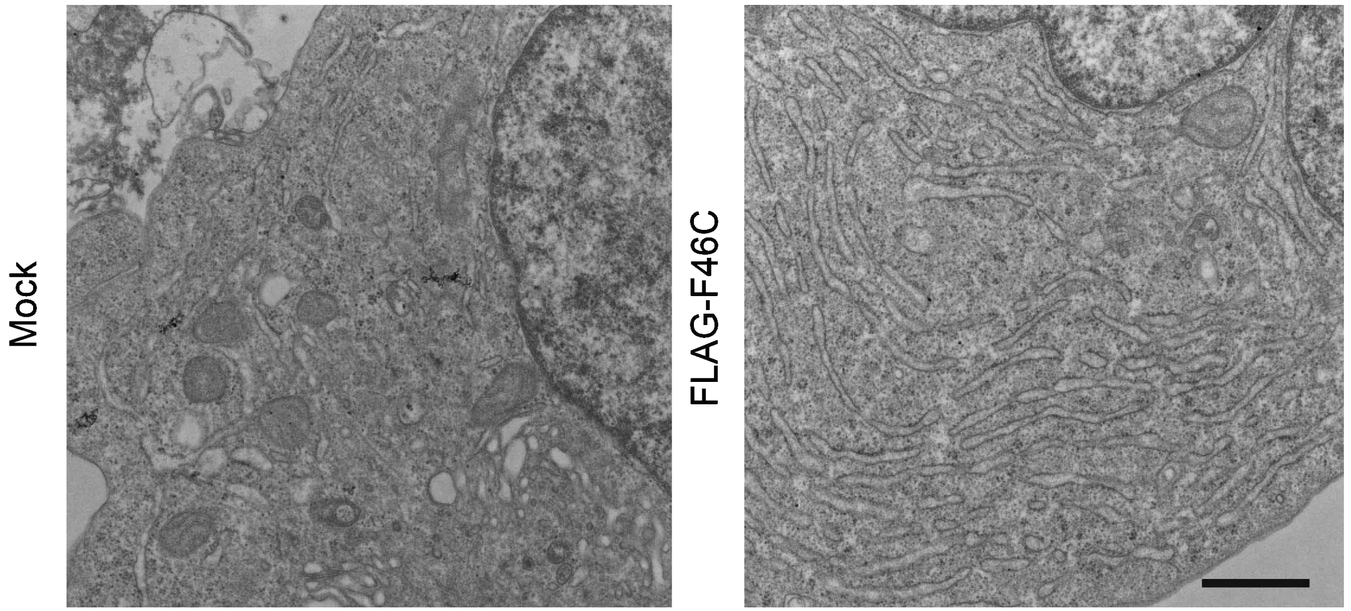
FAM46C boosts the secretory apparatus

FAM46C Silencing in WT RPMI 8266



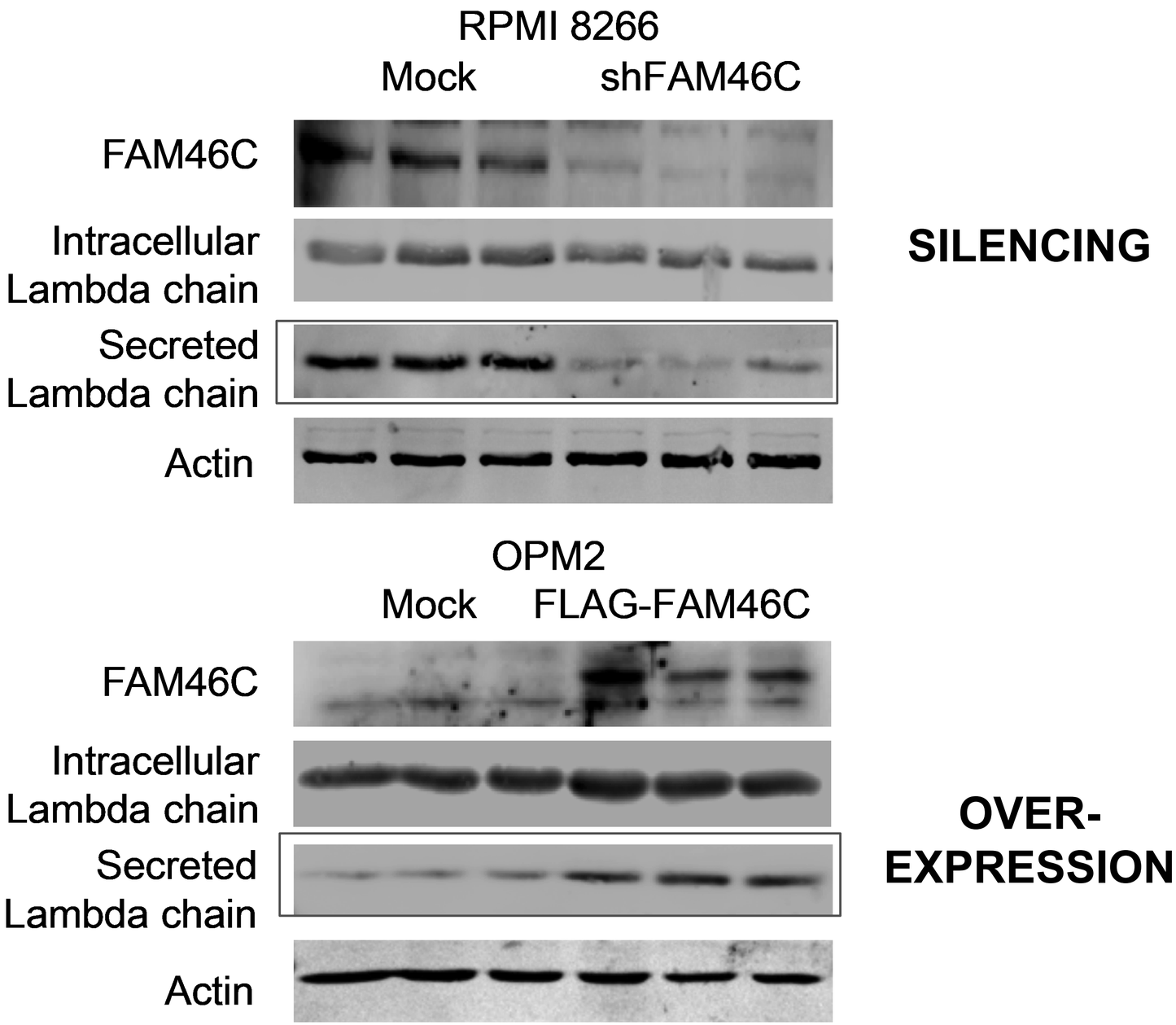
SILAC proteomic

FAM46C Over-expression in OPM2 mut cells

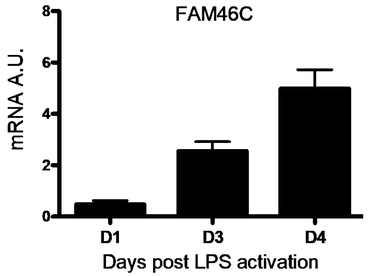


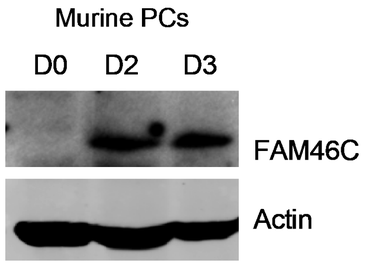
Electron Microscopy

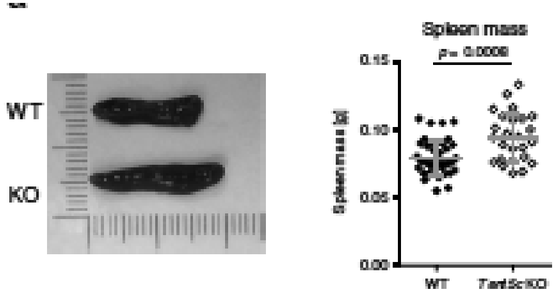
FAM46C promotes Ig production and secretion



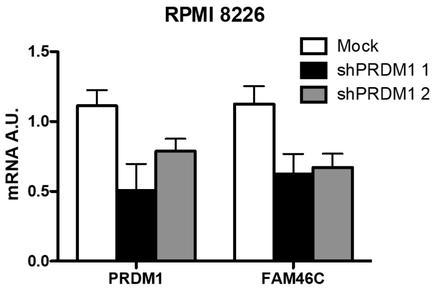
FAM46C is induced under PRDM1 during plasma cell differentiation and sustains antibody production in vivo



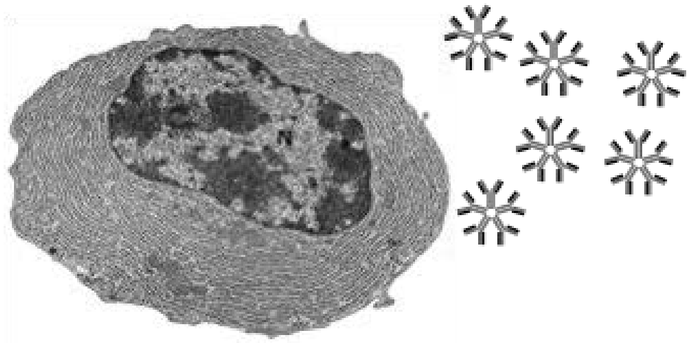




Bilska et al.; Nat Commun 2020



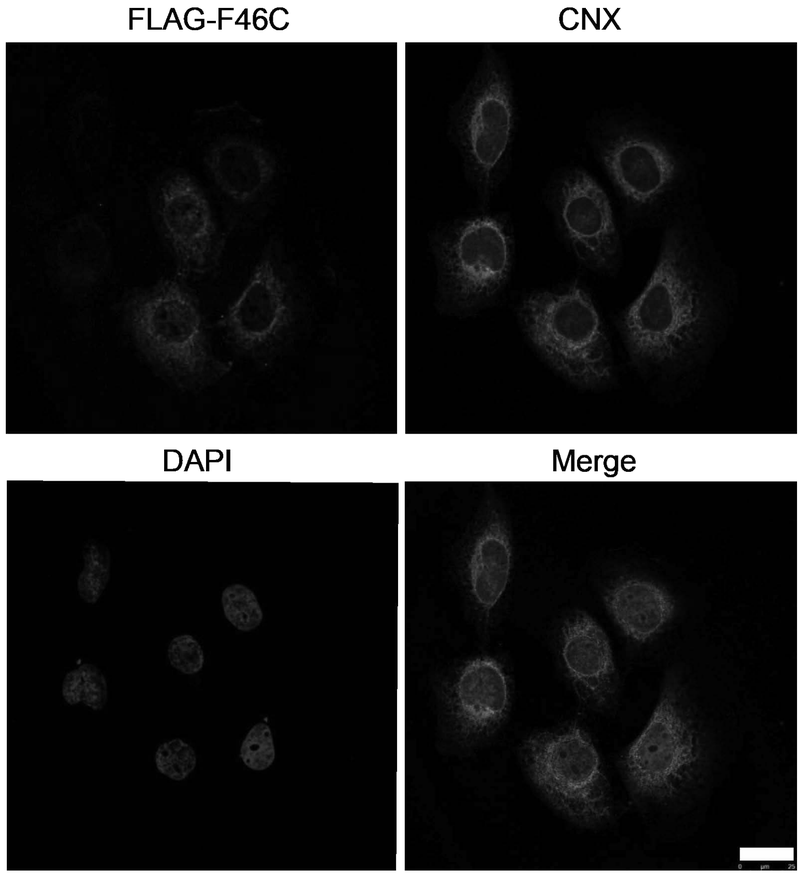
Fucci et al.; Cell Reports 2020



FAM46C −/− mice produce **fewer antibodies** despite having more CD138high plasma cells as a consequence of **accelerated differentiation**.

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



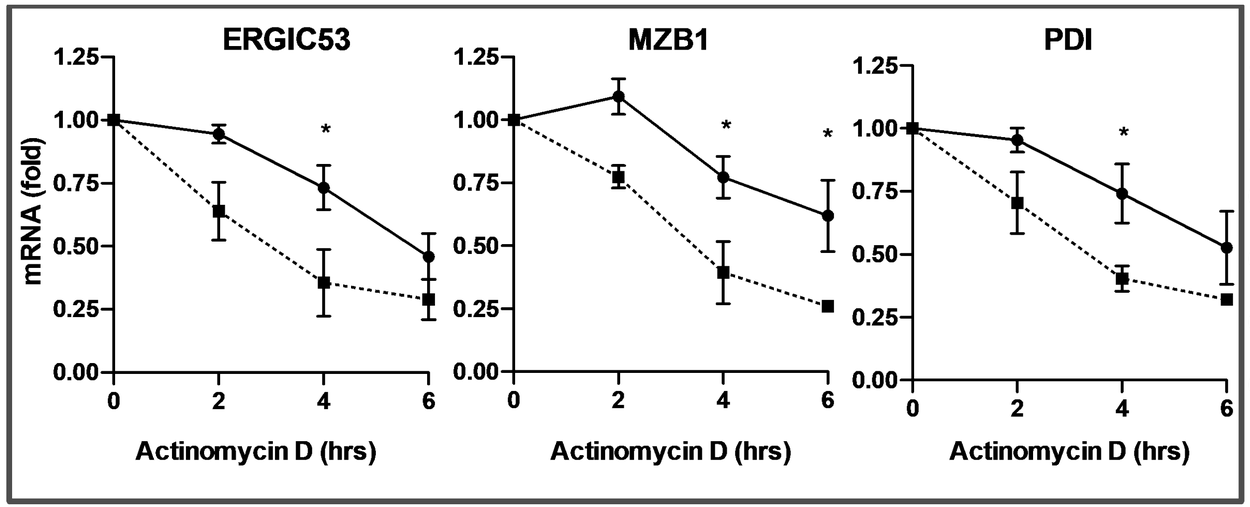
FAM46C interactome

Protein	Control IP	FAM46C IP
FAM46C		**49**
HYOU1	10	25
PABPC4		**8**
SLC25A3	4	11
PABPC1	3	**9**
SQSTM1		**4**
XPOT		4
FNDC3B		**4**
GARS		3
DNAJC11		3
SLC7A5		3
CALR		3
ITGB7		3
CTU2		3

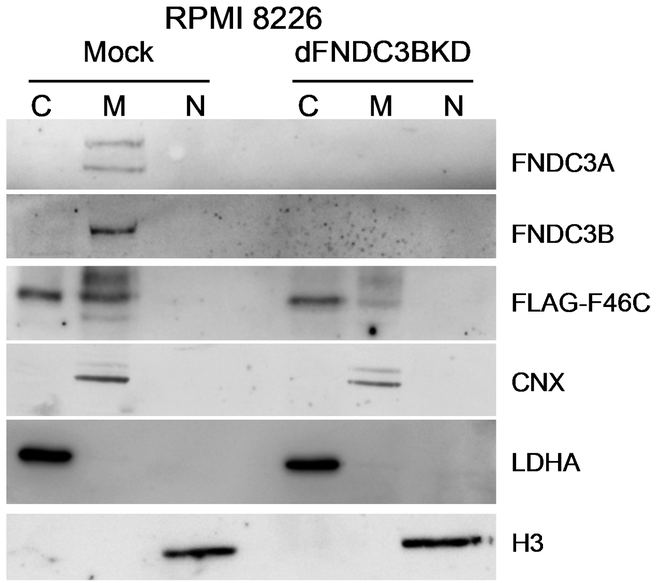
FAM46C interacts with the ER transmembrane proteins **FNDC3A** and **FNDC3B**

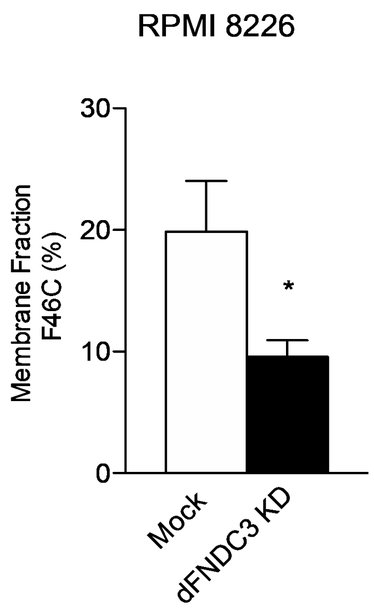
Fucci et al.; Cell Reports 2020

FNDC3 proteins are required for FAM46C localization and activity

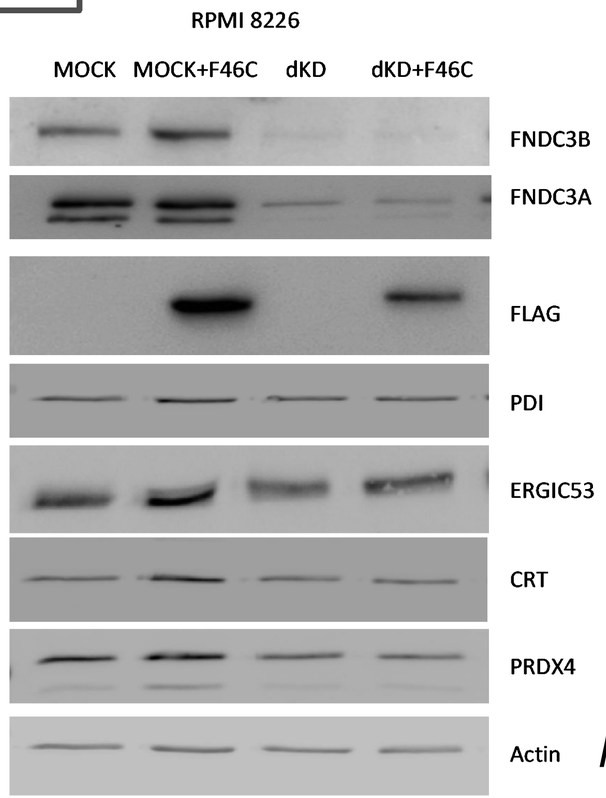


mRNA stability





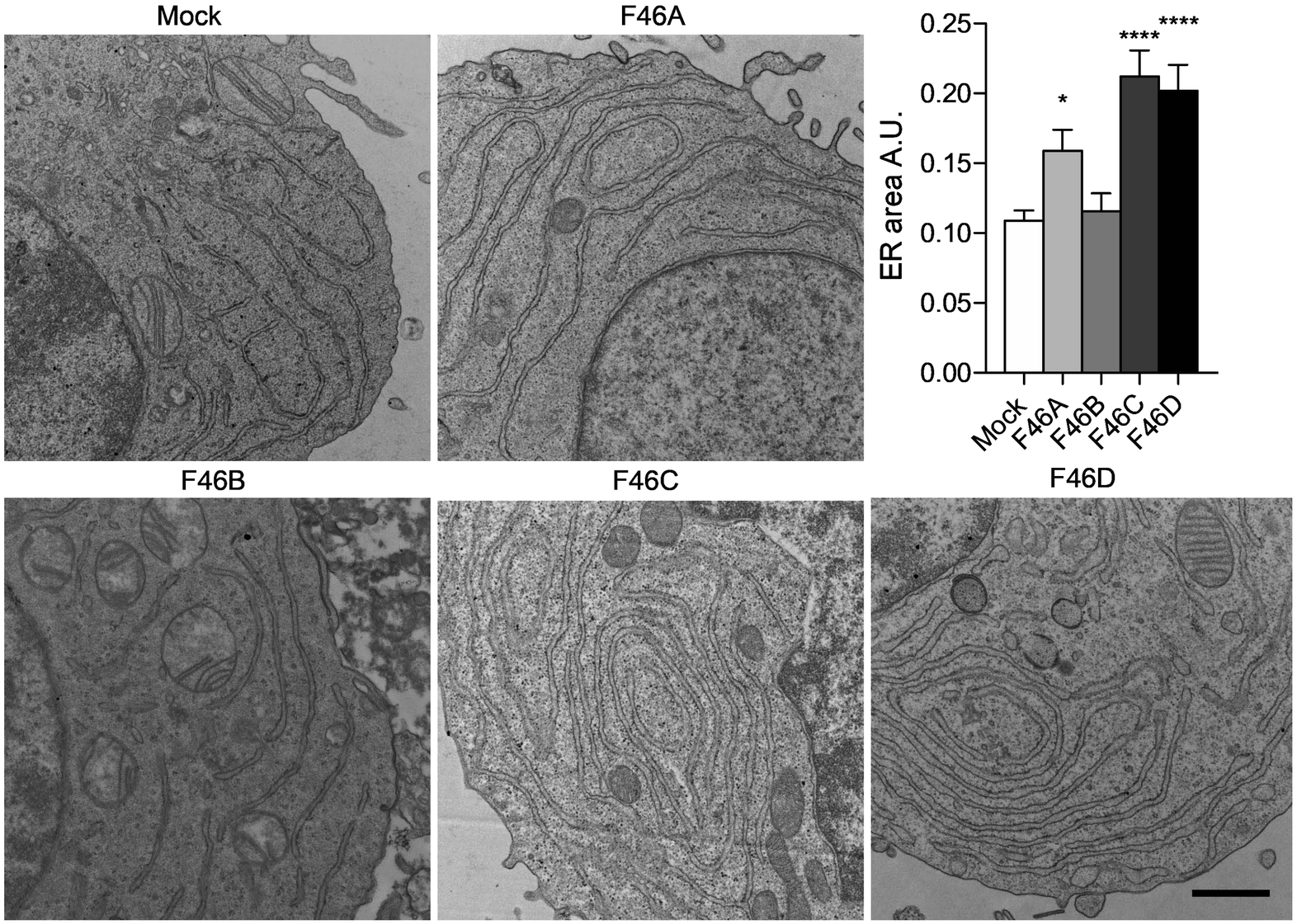
ER localization



ER protein levels

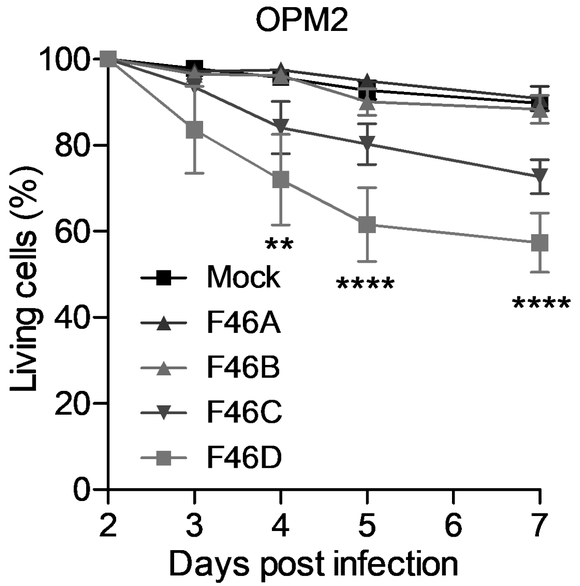
Fucci et al.; Cell Reports 2020

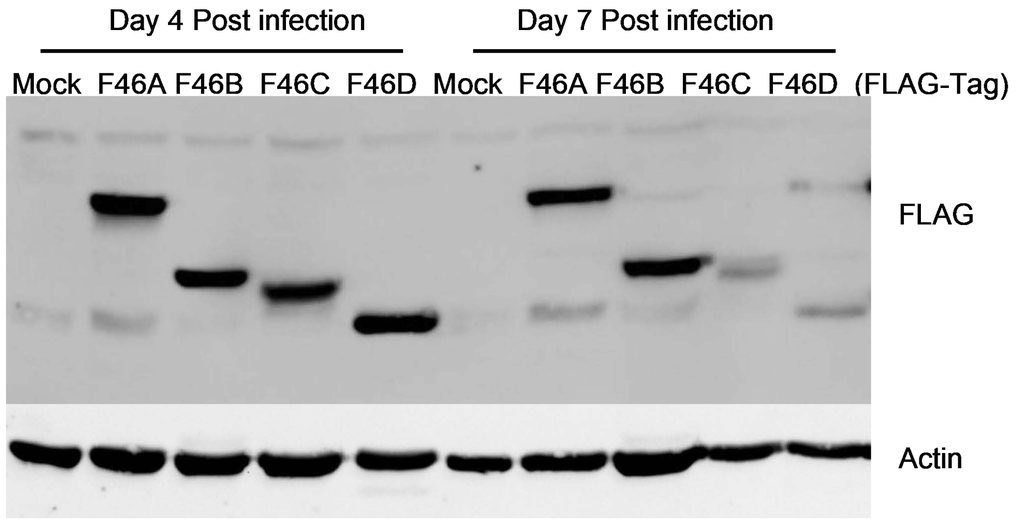
FAM46 members differ in their effects on ER

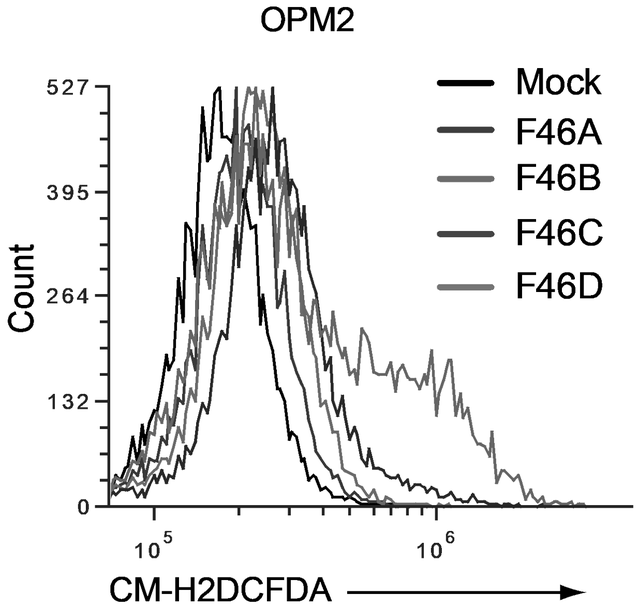


FAM46C and **FAM46D** have the most potent effects on the ER

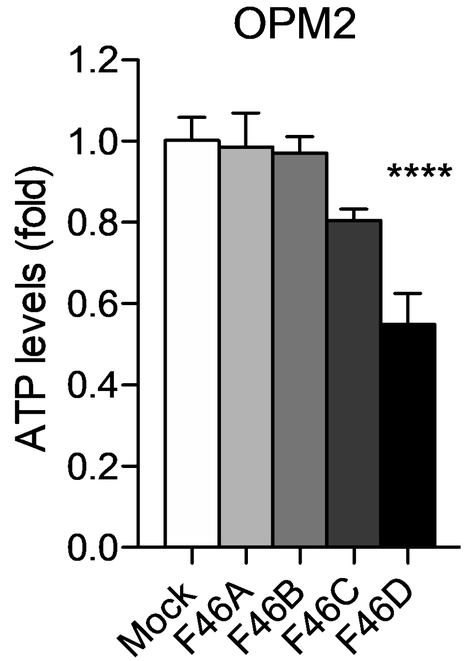
FAM46C and FAM46D boost secretion beyond sustainability







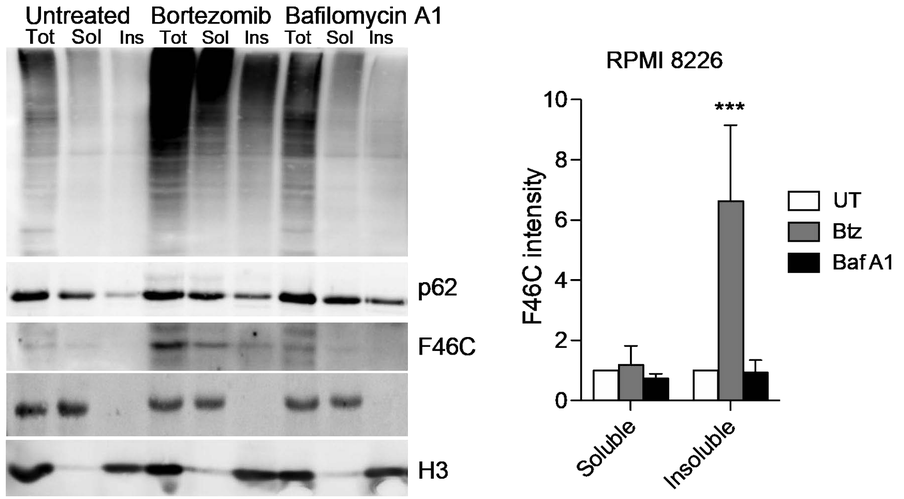
ROS levels



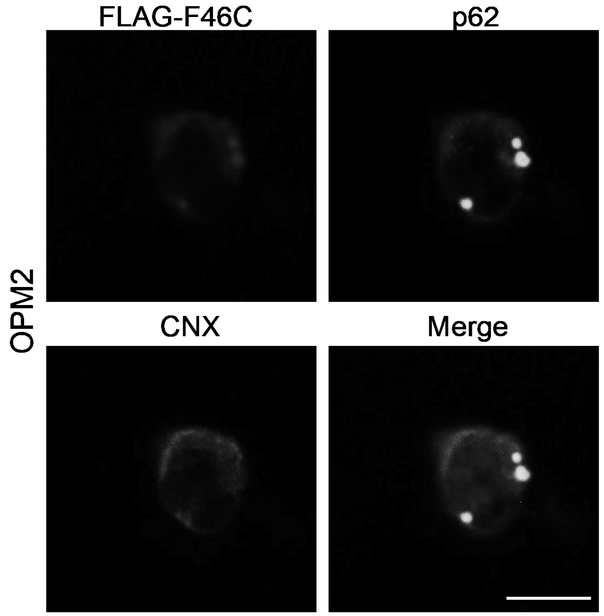
ATP levels

FAM46C is tightly regulated by degradative pathways

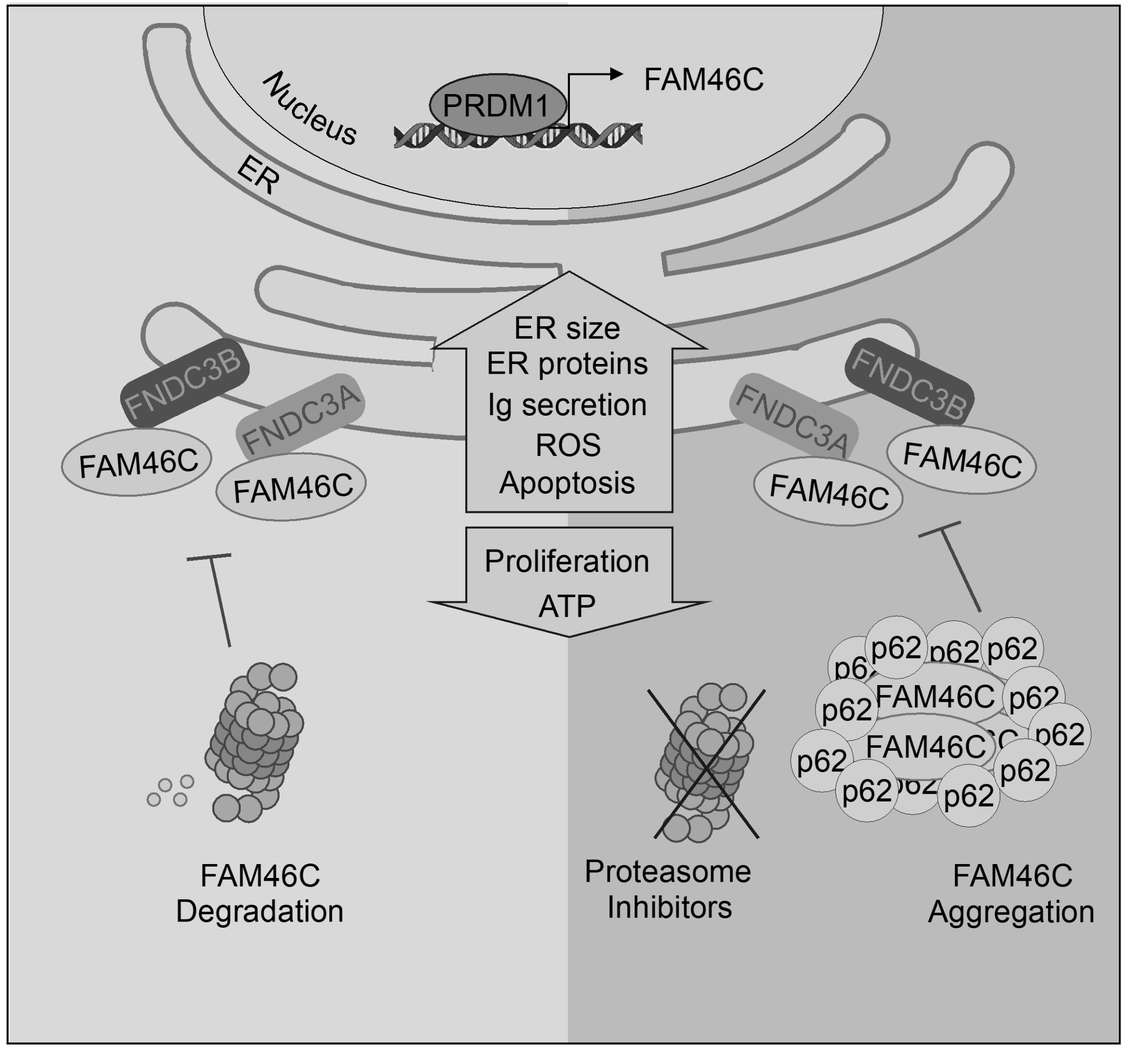
1) FAM46C is rapidly **degraded by the Ubiquitin Proteasome System** (UPS)



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



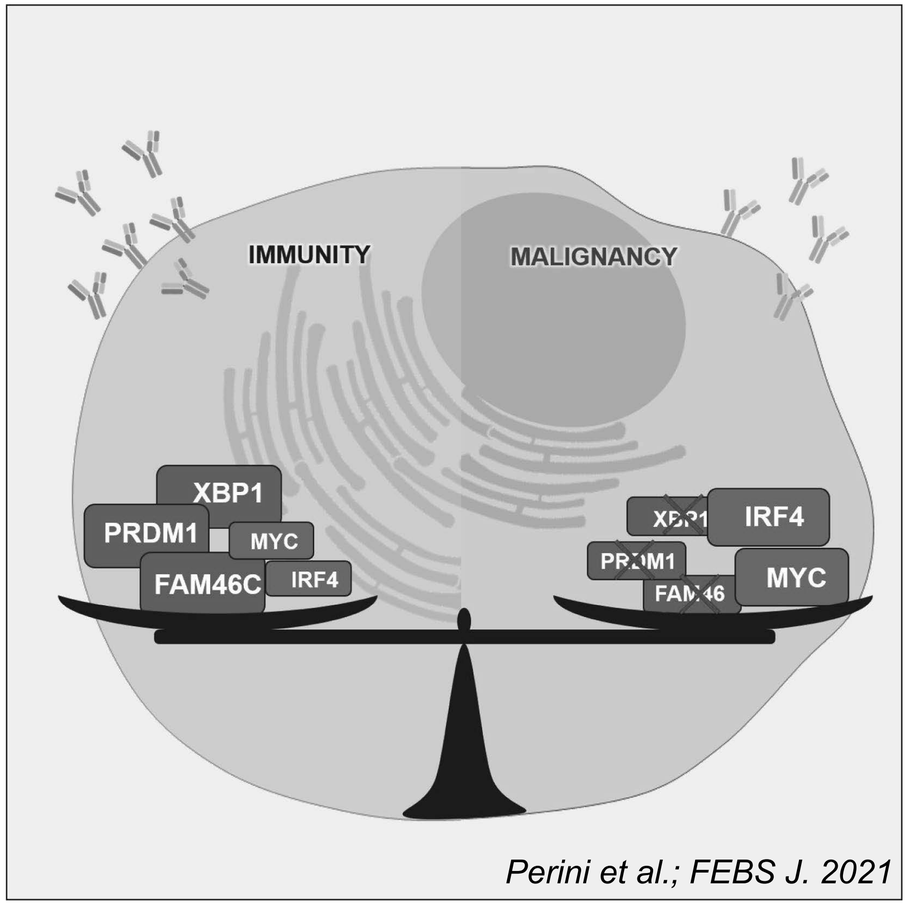
Conclusions



Fucci et al.; Cell Reports 2020

- 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

Immunity vs Malignancy



Perini et al.; FEBS J. 2021

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?

Acknowledgements

Cencilab:

Simone Cenci
Ugo Orfanelli
Tommaso Perini
Massimo Resnati
Monica Fabbri
Lorenzo Fumagalli
Andrea Locatelli
Maria Materozzi
Laura Oliva
Matteo Trudu

Former Members:

Chiara Fucci
Elena Riva
Elena Ruggieri
Floriana Cremasco
Francesca Paradiso

Collaborators:

Luca Rampoldi
Andrea Raimondi
Annapaola Andolfo

Mario Nuvolone
(Policlinico San Matteo, Pavia)

Angela Bachi (IFOM)

Stefano Biffo (INGM)
Nicola Manfrini

Multiple Myeloma Research Foundation, OSR SEED Grant, International Myeloma Foundation, Fondazione Cariplo

MULTIPLE MYELOMA Research Foundation

INTERNATIONAL MYELOMA FOUNDATION

OSPEDALE SAN RAFFAELE

Fondazione CARIPLO