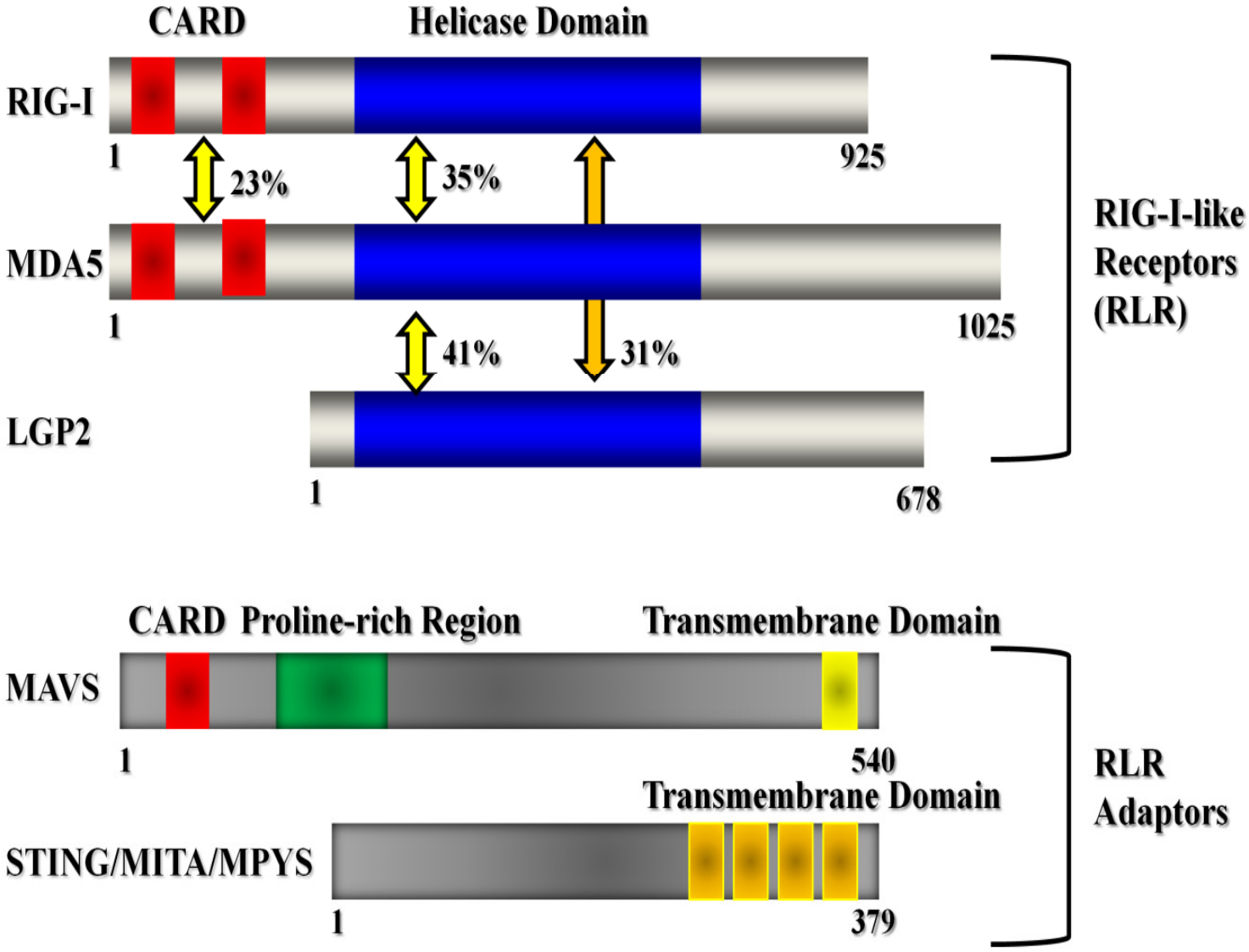
Regulation of STING Expression via the RIG-I Dependent RNA Sensing Pathway

Vaccines-2014
Valencia, Spain
September 24, 2014

Rongtuan Lin

Lady Davis Institute for Medical Research
Department of Medicine
McGill University, Montreal, CANADA

Retinoic acid-inducible gene-I (RIG-I)-like receptors (RLRs) and their downstream adaptors



Superfamily 2 DExD/H-Box RNA Helicases

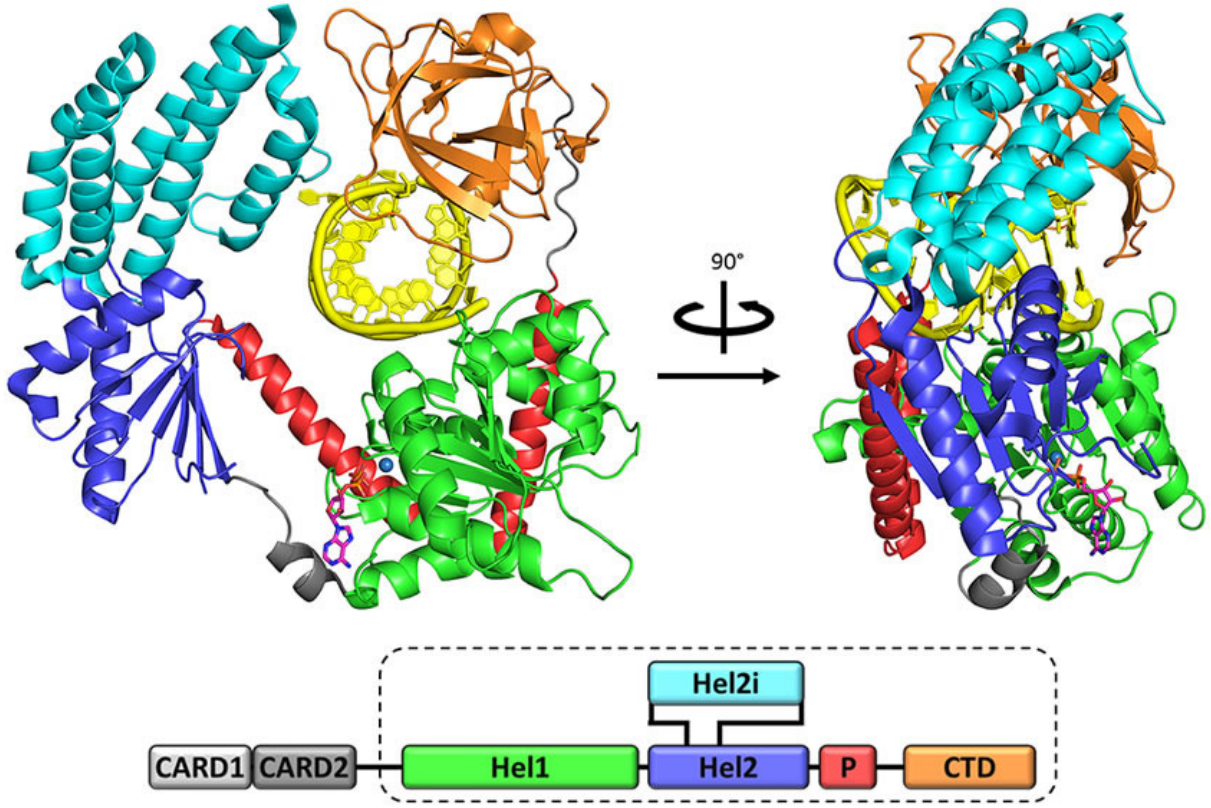
A

RIG-I

MDA5

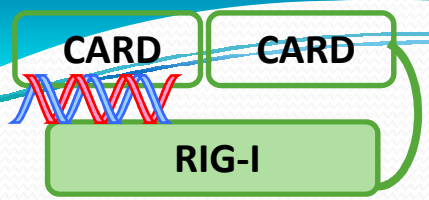
LGP2

RIG-I



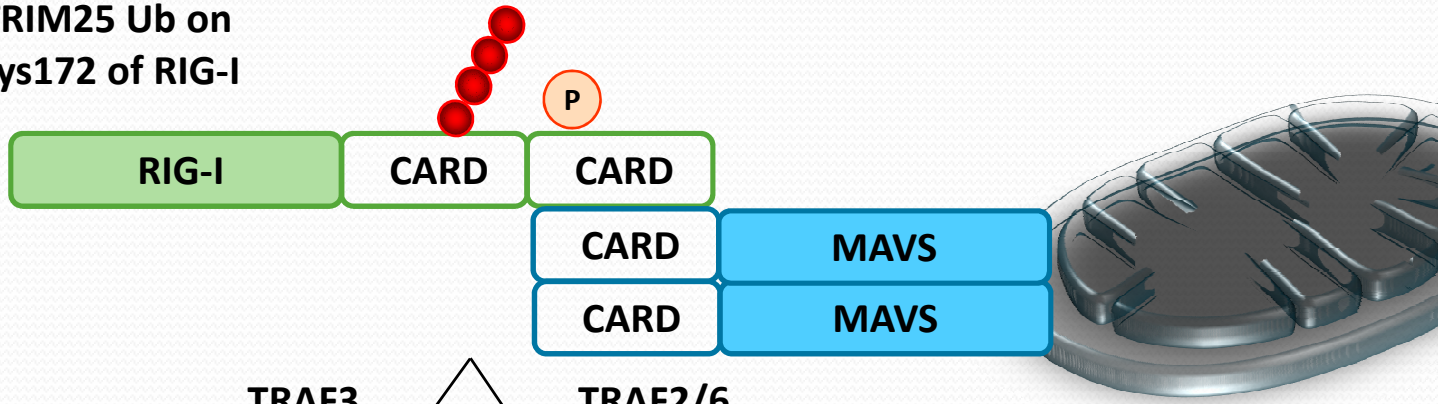
http://www.hhmi.org/research/rna-tertiary-structure-and-recognition-proteins
http://www.cell.com/action/showImagesData?pii=S1074-7613%2813%2900204-5

RIG-I Signaling



Conformational change

TRIM25 Ub on Lys172 of RIG-I



TRAF3
NEMO
TANK

TRAF2/6
RIP1
NEMO

Non-canonical kinases activation

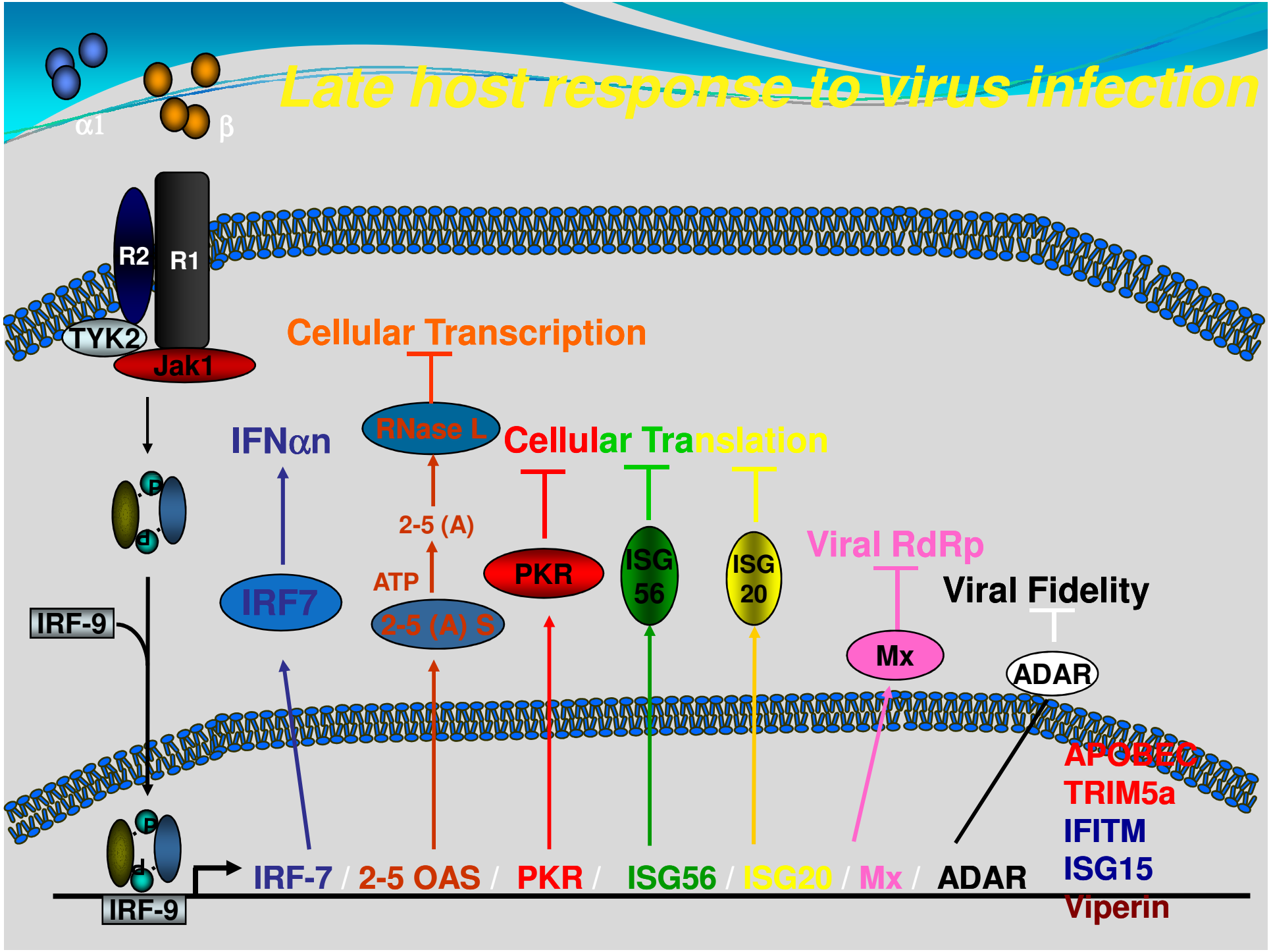
Canonical kinases activation

IRF activation

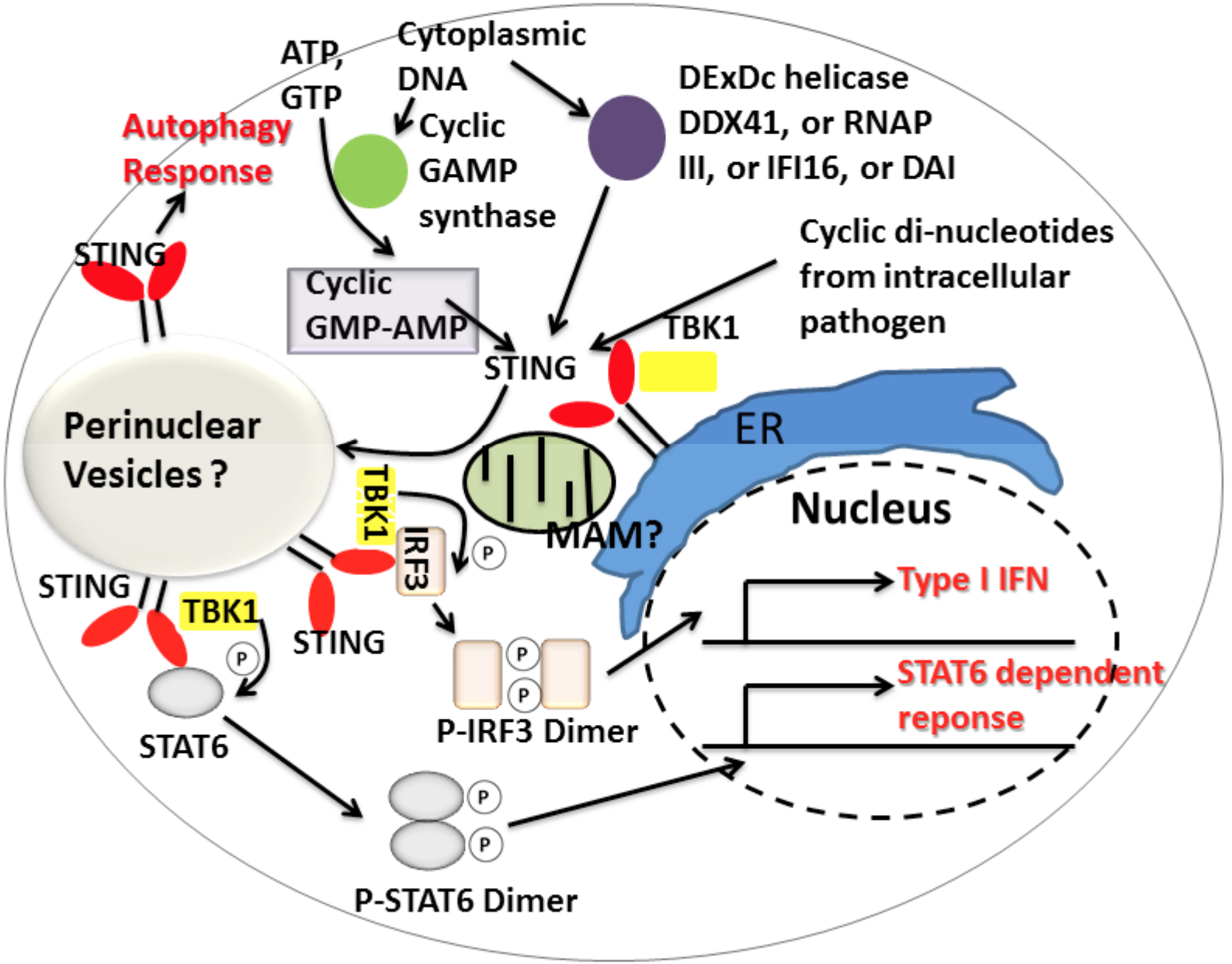
NF-κB activation

Type I IFNs

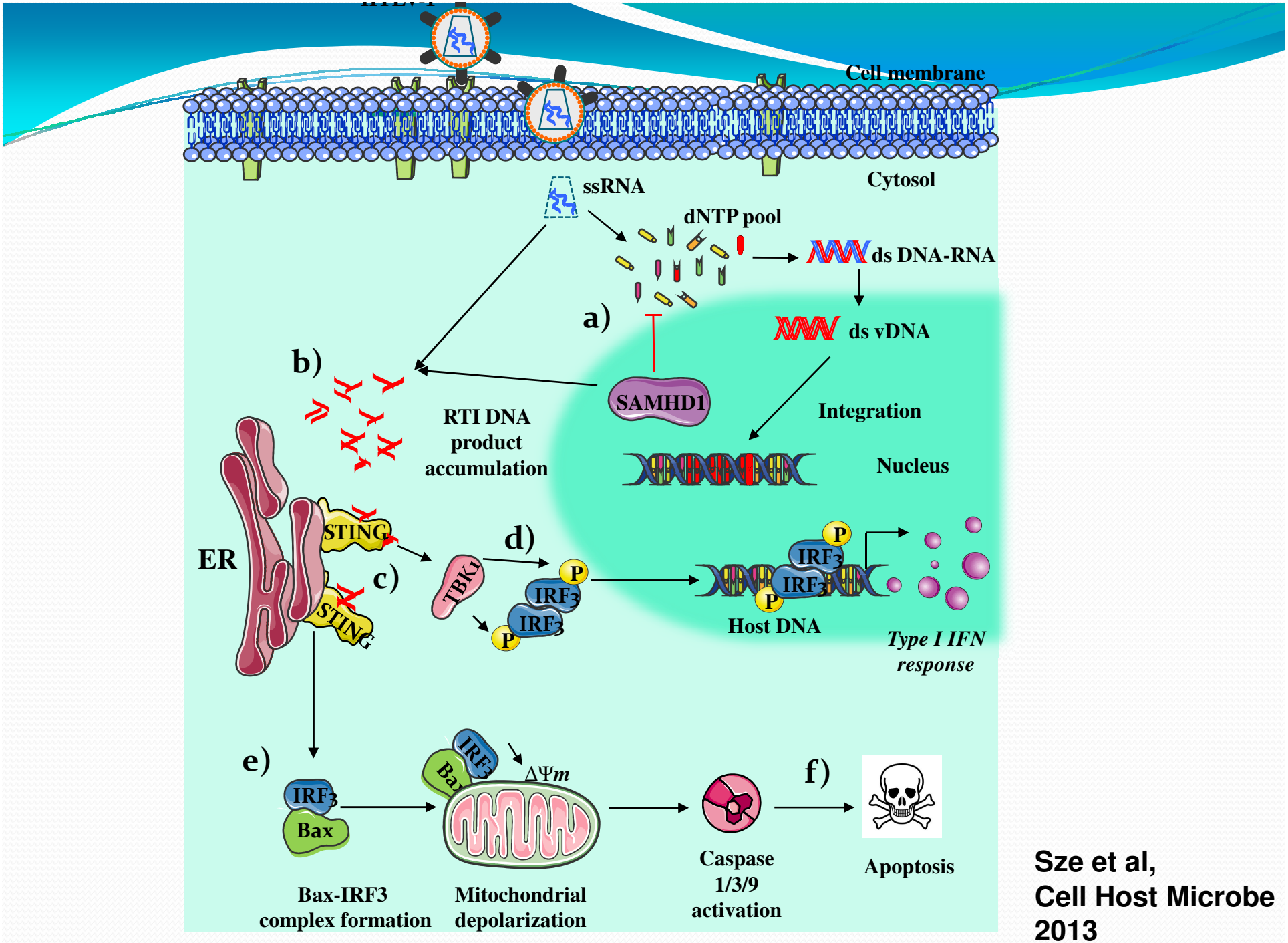
Inflammatory Cytokines


Late host response to virus infection
α1
β
R2
R1
TYK2
Jak1
Cellular Transcription
IFNαn
RNase L
Cellular Translation
2-5 (A)
ATP
PKR
ISG 56
ISG 20
Viral RdRp
Viral Fidelity
IRF7
2-5 (A) S
Mx
ADAR
IRF-9
IRF-7 / 2-5 OAS / PKR / ISG56 / ISG20 / Mx / ADAR
APOBEC
TRIM5a
IFITM
ISG15
Viperin
IRF-9

Overview of STING Signaling

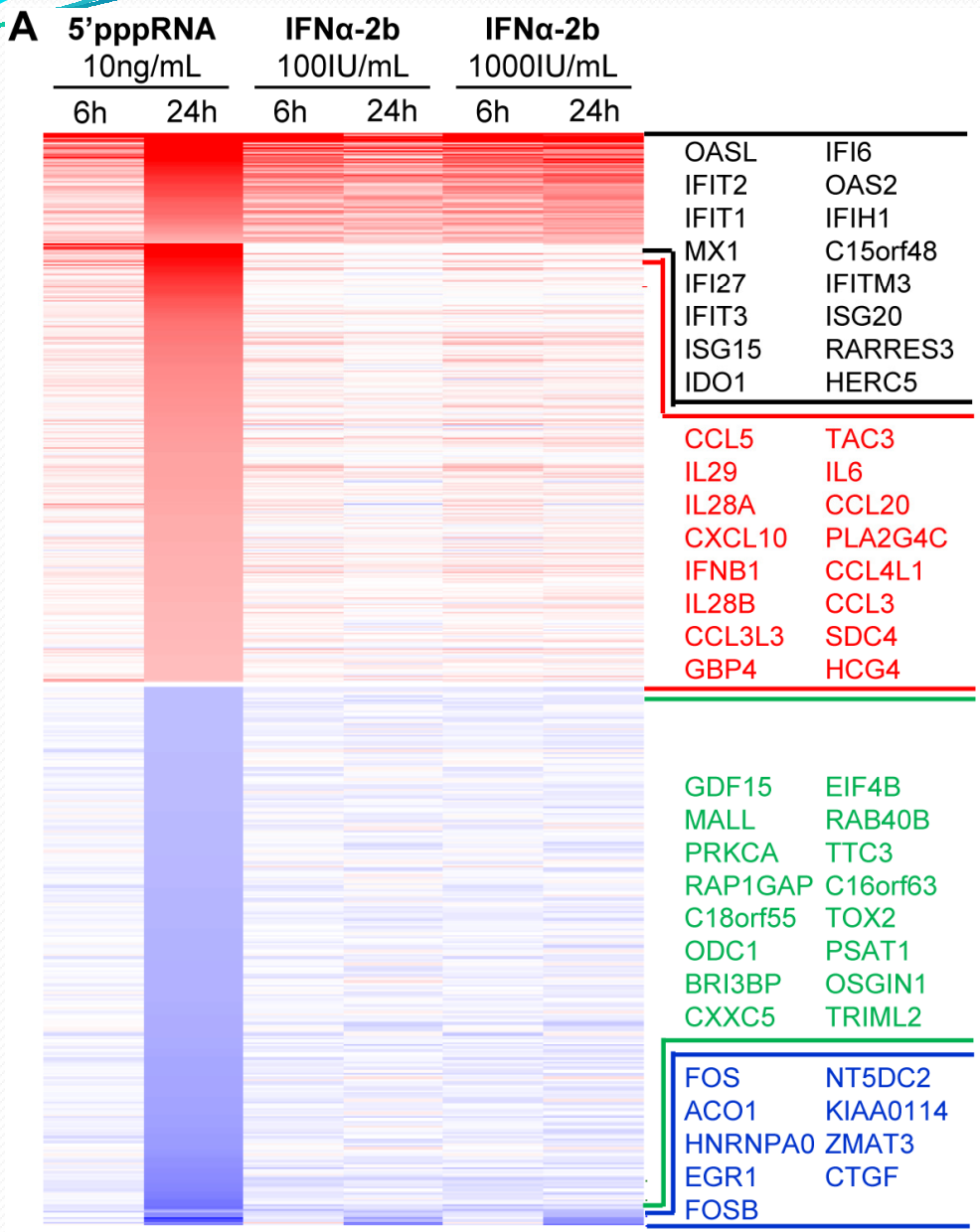


wikipedia/commons/thumb/a/a6/STING_signaling_20130422.png/420px-STING_signaling_20130422.png

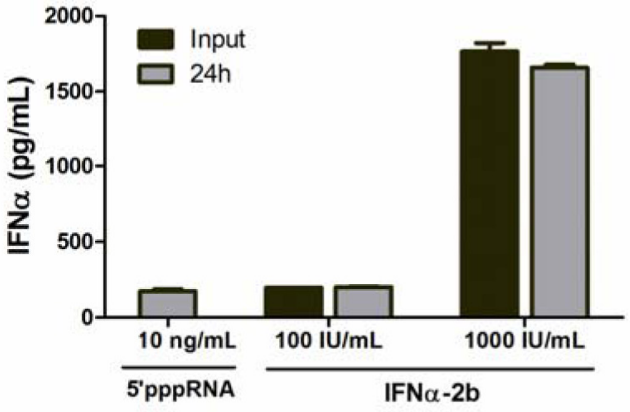


Sze et al,
Cell Host Microbe
2013

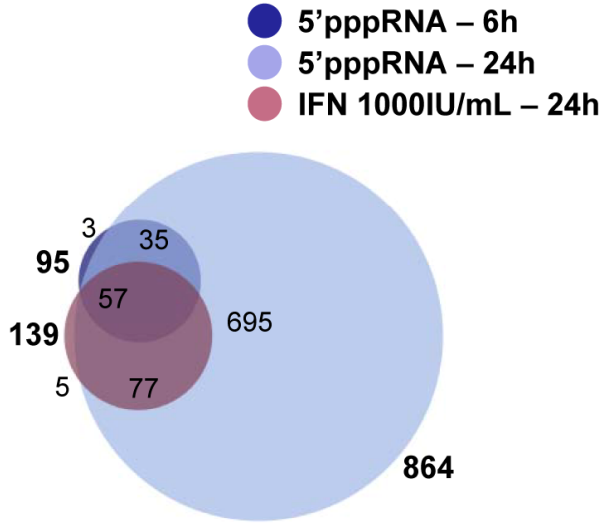
Comparison of 5'pppRNA and interferon



B

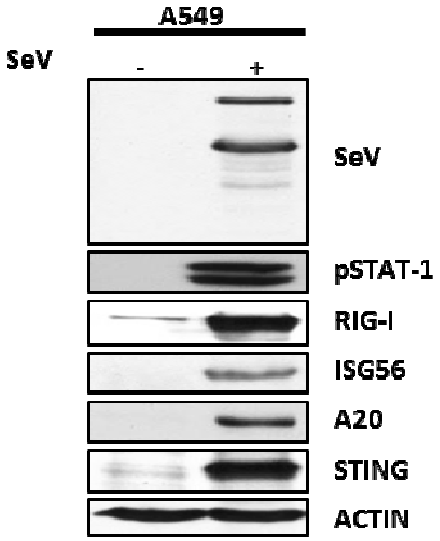


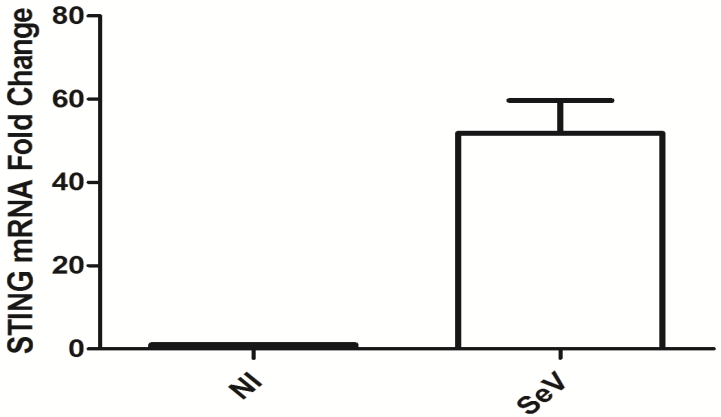
C

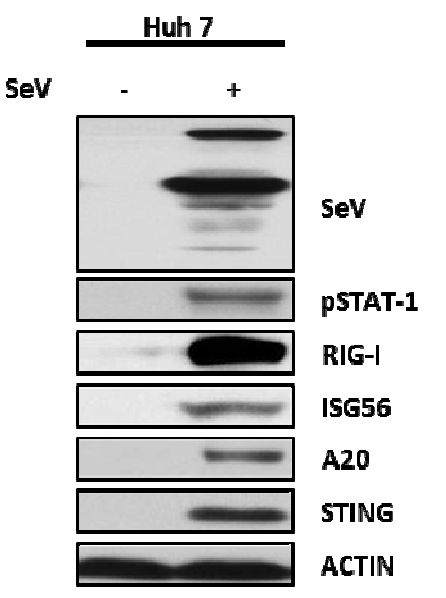


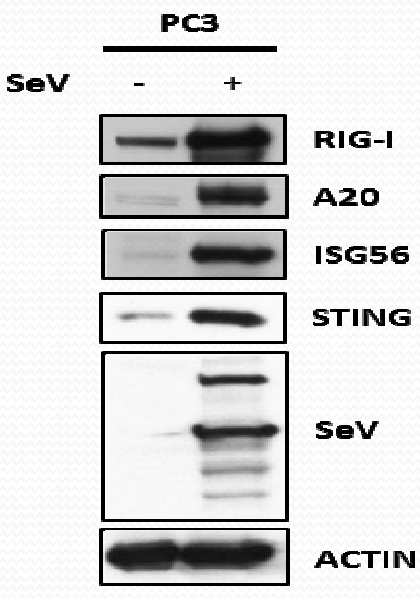
Goulet et al., PloS Pathog. 2013

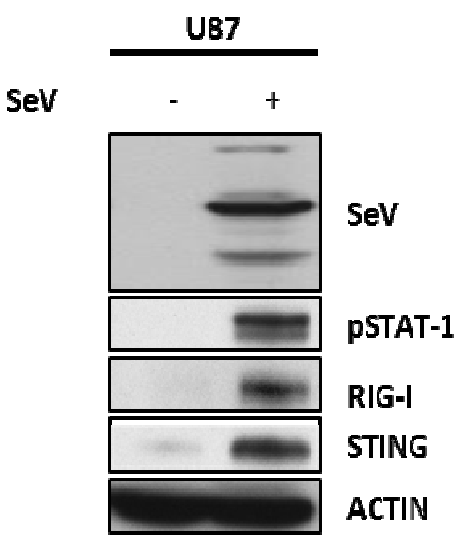
Sendai virus (SeV) infection induces STING expression in various cells



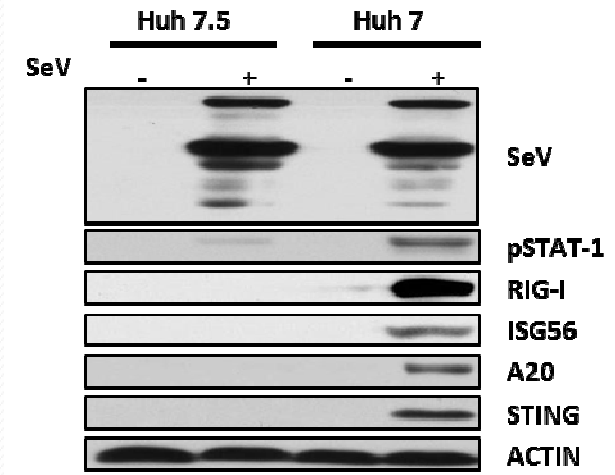


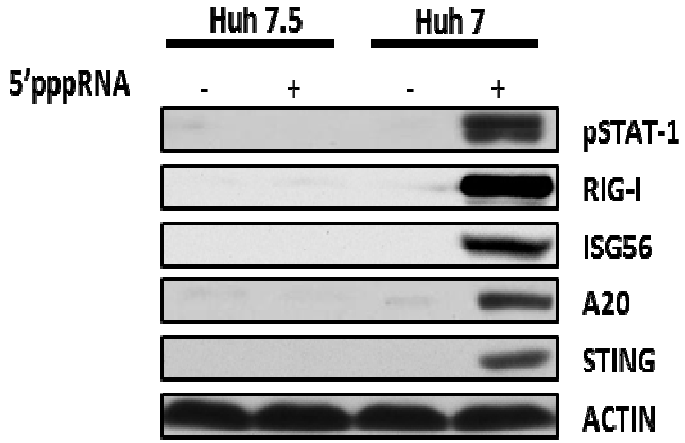


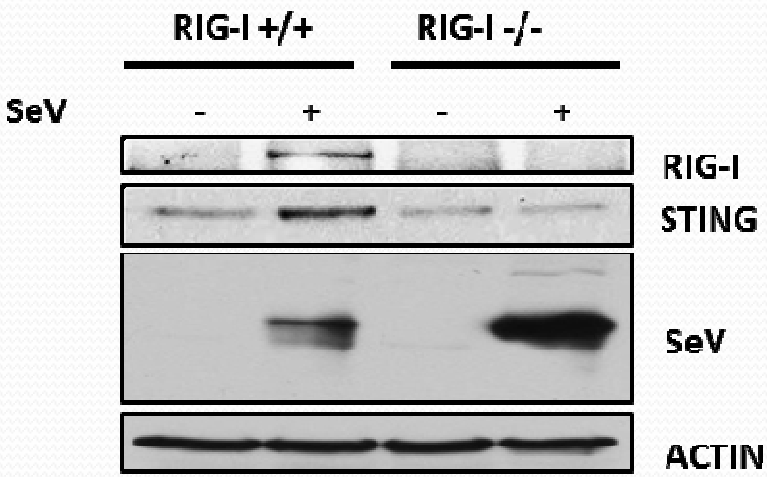


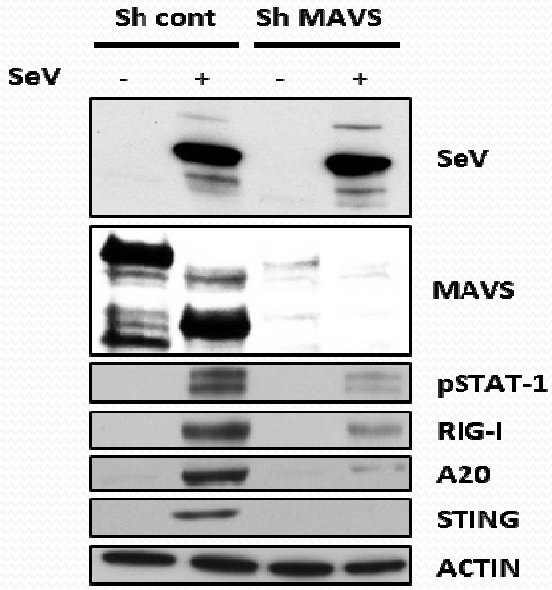


STING up-regulation requires functional RIG-I signalling

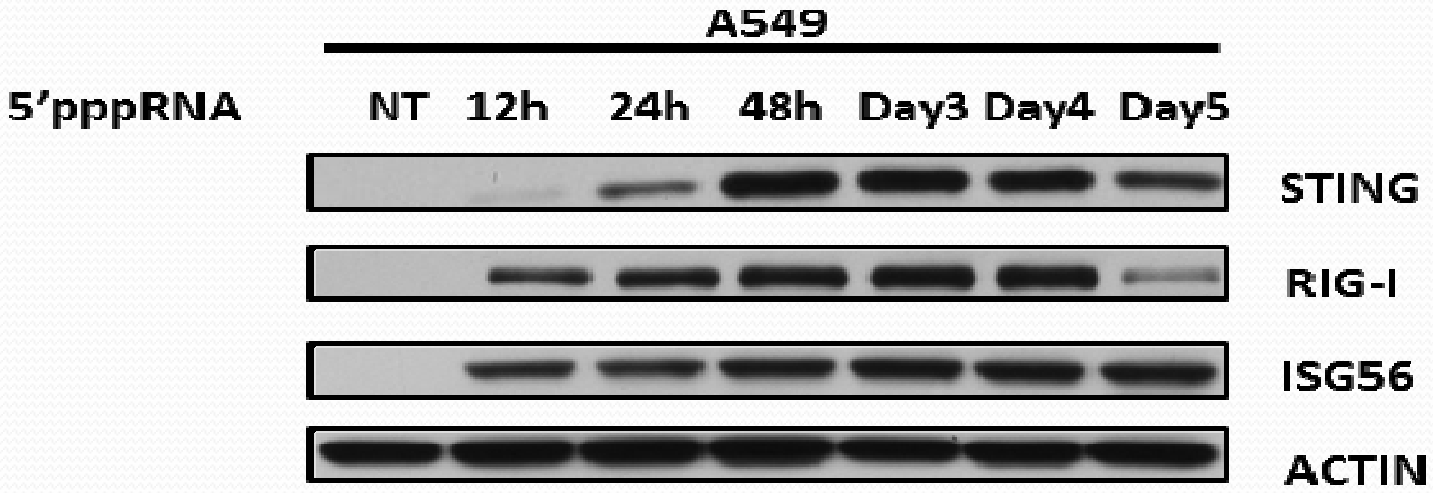


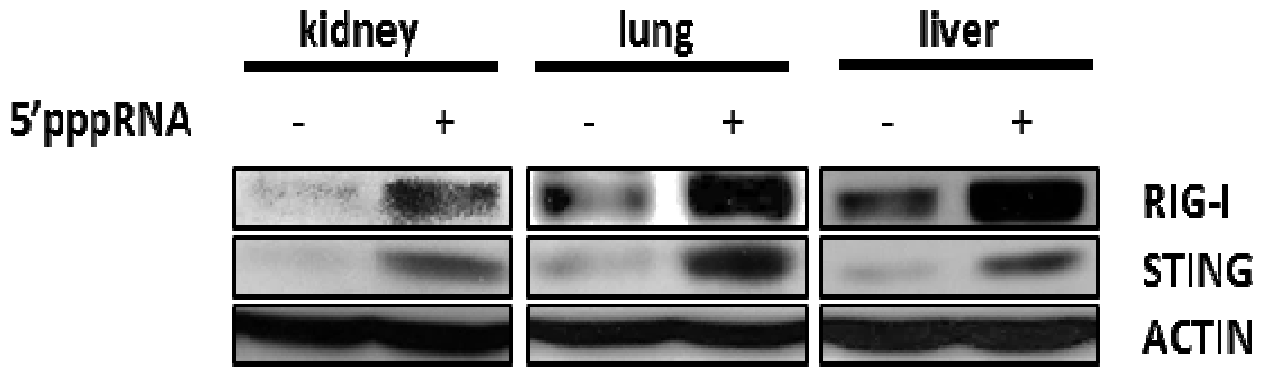




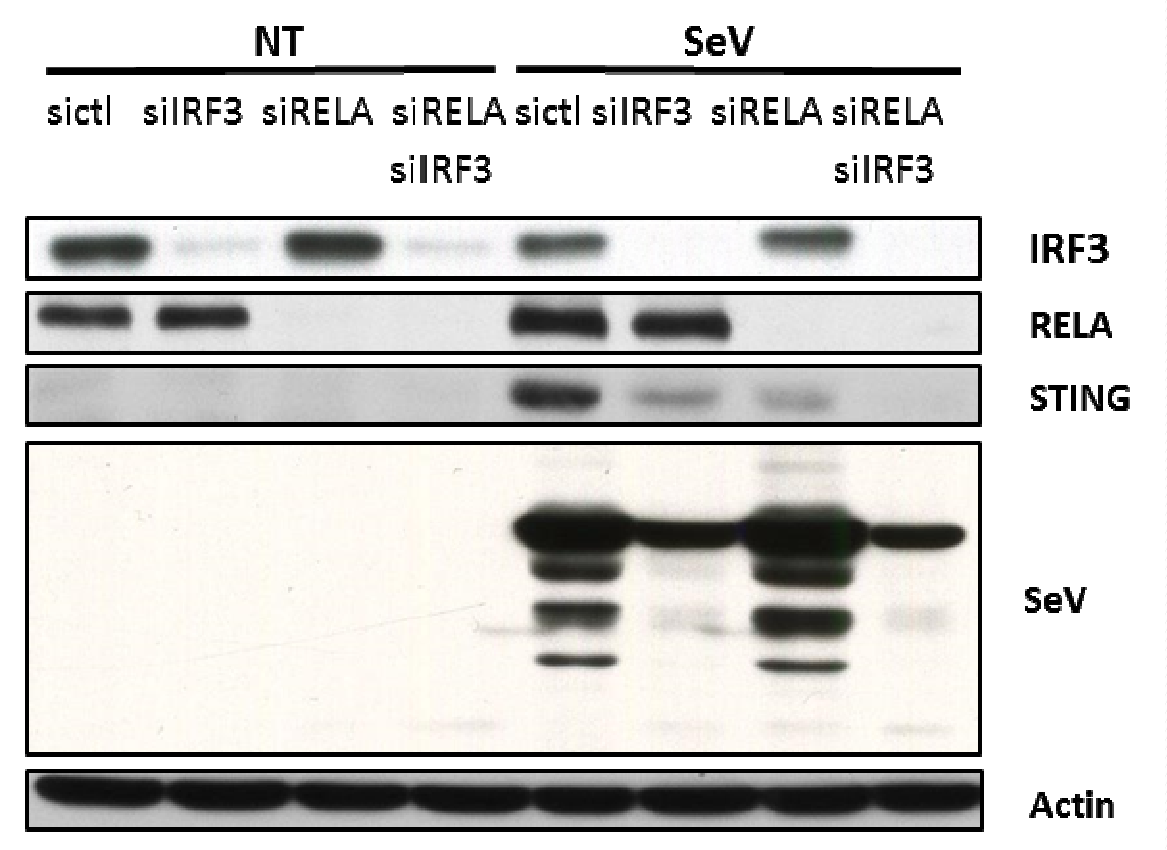


RIG-I agonist 5'ppp RNA triggers STING activation both in vitro and in vivo

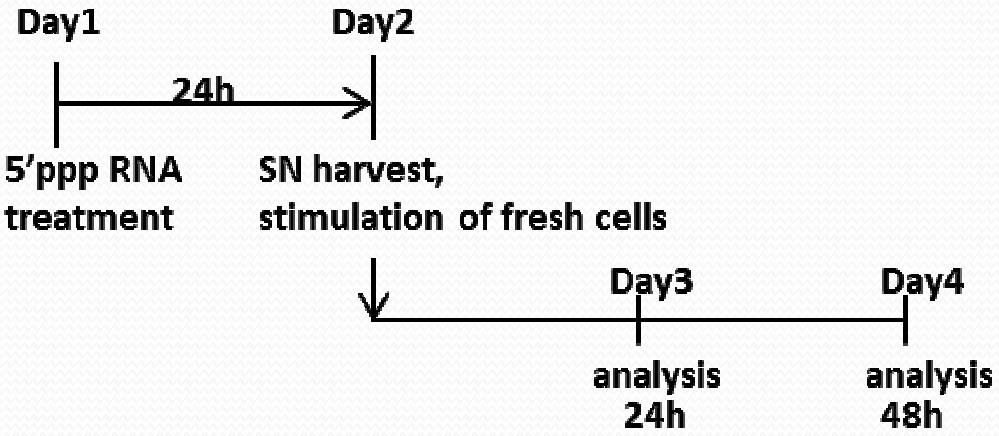


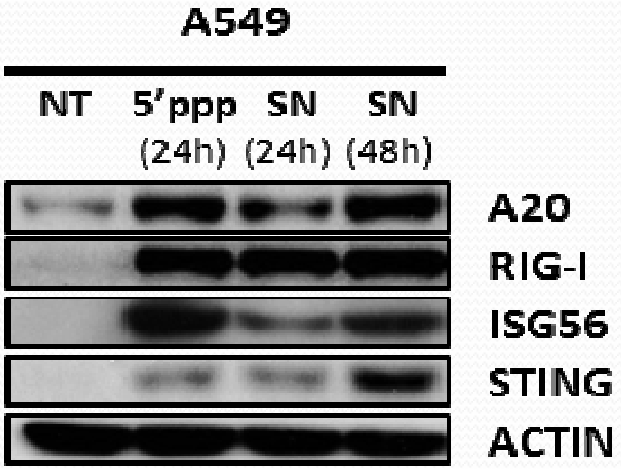


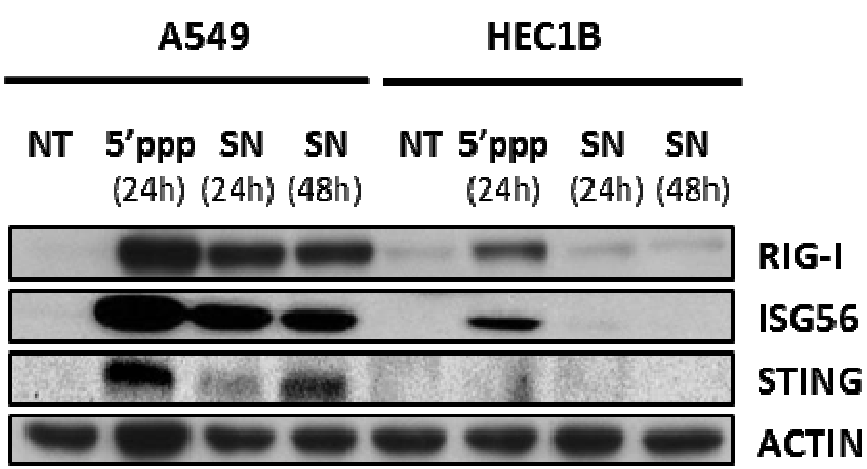
Transcription factors RelA and IRF3 are involved in mediating the induction of STING



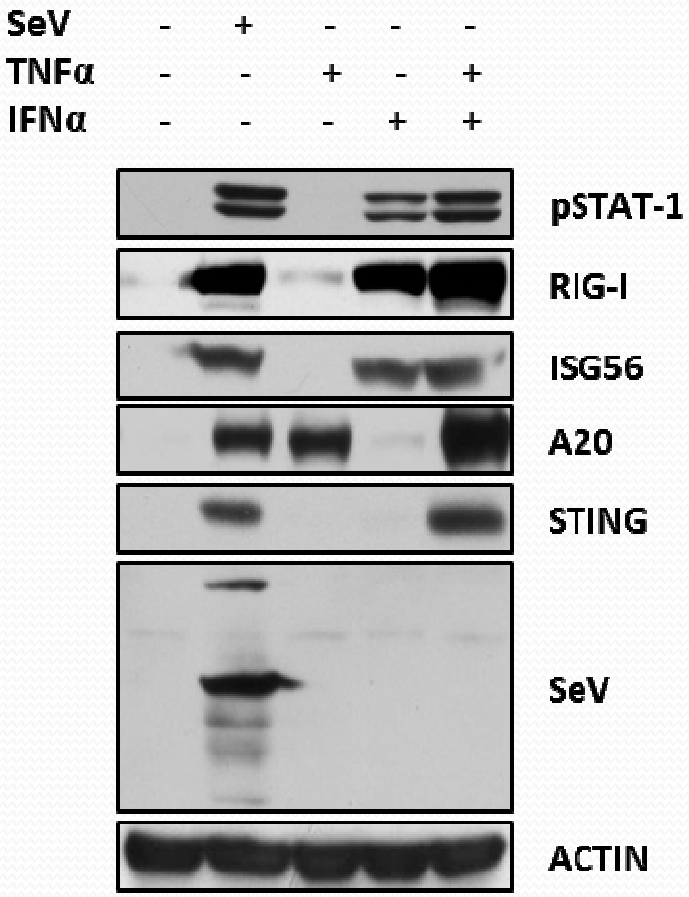
5'ppp RNA-induced STING expression results from an autocrine/paracrine mechanism

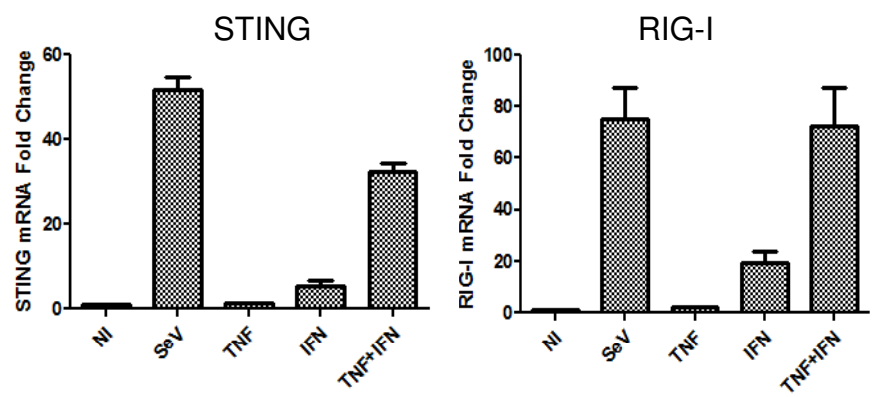


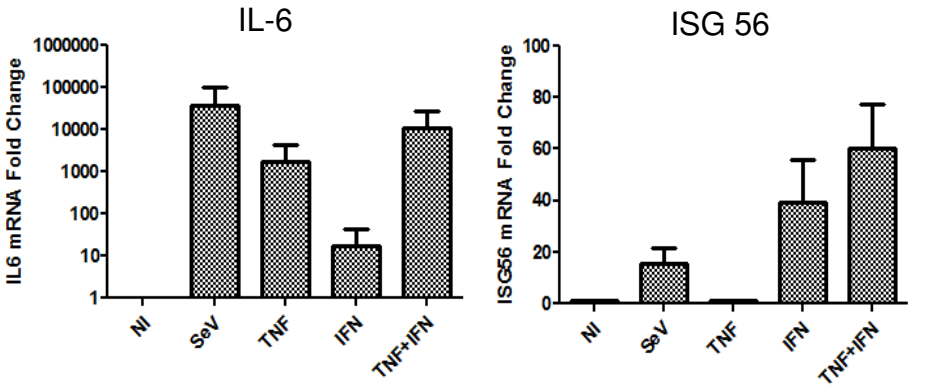




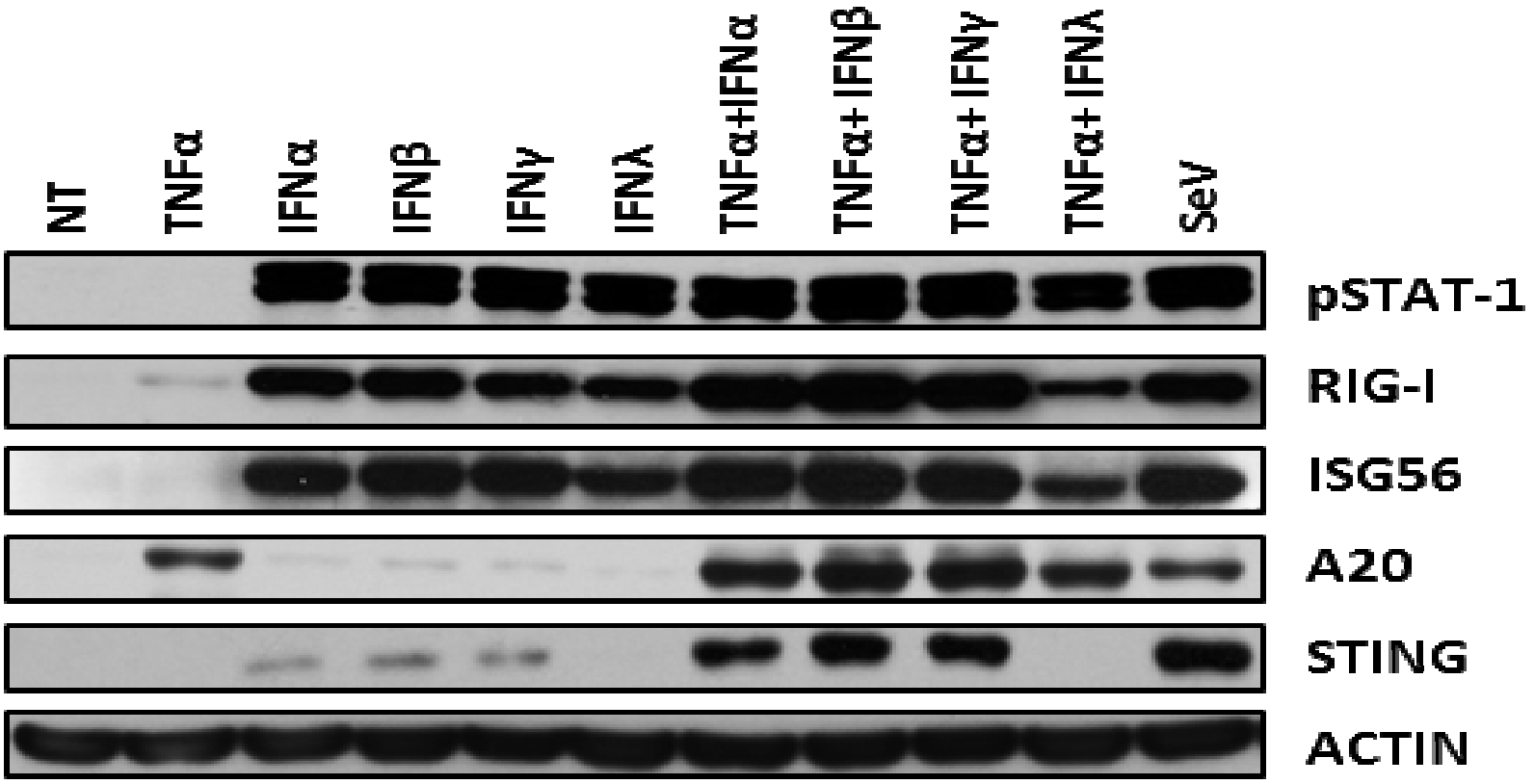
TNF-α and IFN-α synergize to induce STING expression



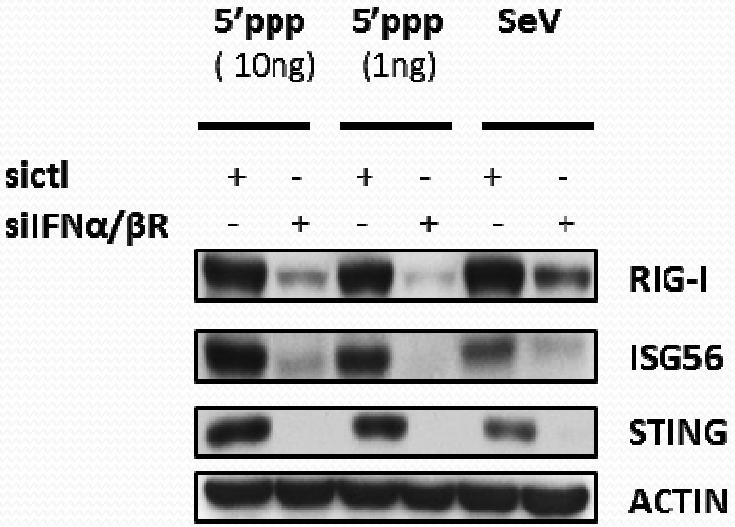


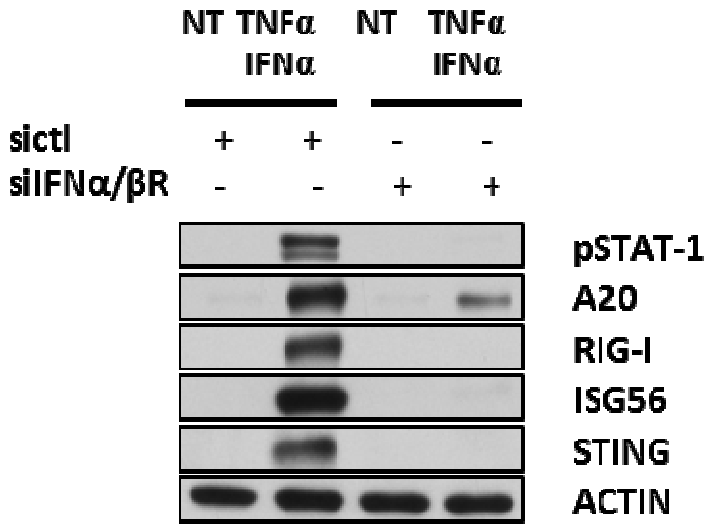


Modulation of STING expression by individual or combination of cytokines



Depletion of IFNα/βR and STAT1 abolished STING protein expression







Conclusions

Our data demonstrate that:

- Sendai virus infection induces STING expression at both the mRNA and protein levels in various cell types
- STING induction is dependent on functional RIG-I signaling
- 5'ppp RNA triggers STING expression both in vitro and in vivo
- TNFα and IFN (type I or II) synergistically regulate STING expression

Acknowledgements

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Kazuhiro Iwai - Osaka University
Jianhui Wu – McGill University
David Stojdl – Ottawa University

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