FOOT-AND-MOUTH DISEASE VIRUS MODULATION OF EARLY INNATE IMMUNE RESPONSE IN SWINE

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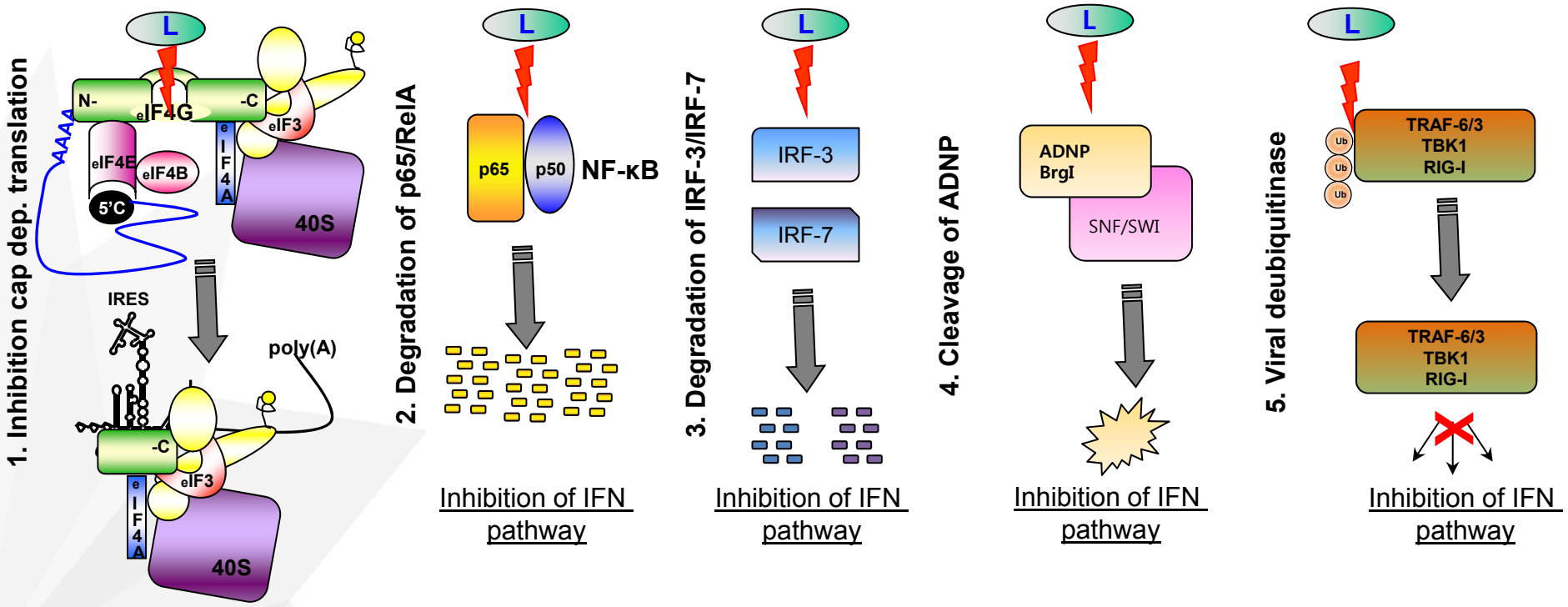
FMDV controls cellular innate response

L^{pro} blocks cellular innate immune response

Removing the leader coding region (leaderless virus) or inserting mutations in some domains within the L^{pro} coding sequence (Chinsangaram et al.. 1998; de los Santos et al.. 2009; Diaz-San Segundo et al.. 2012. Mason et al.. 1997; Piccone et al.. 1995. 2010) resulted in an attenuated virus



Devaney et al.. 1988
Belsham & Brangwyn. 1990

de los Santos et al. 2007

Wang et al.. 2010

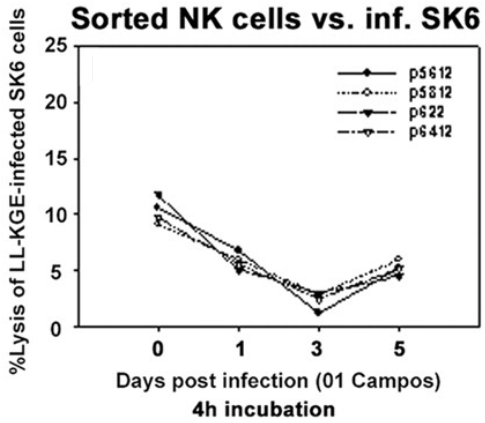
Medina et al, 2017

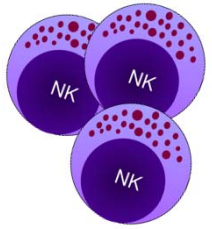
Wang et al.. 2011

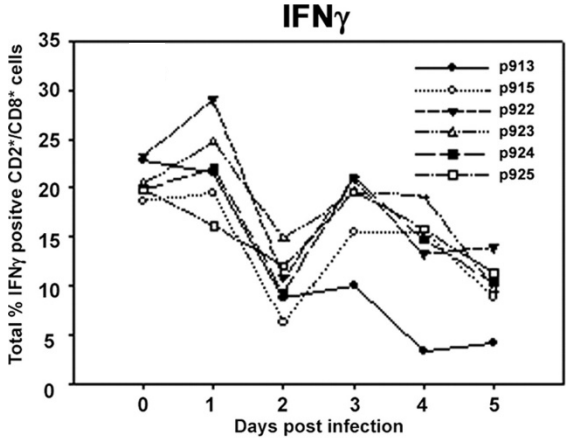
FMDV impairs NK cell lytic activity

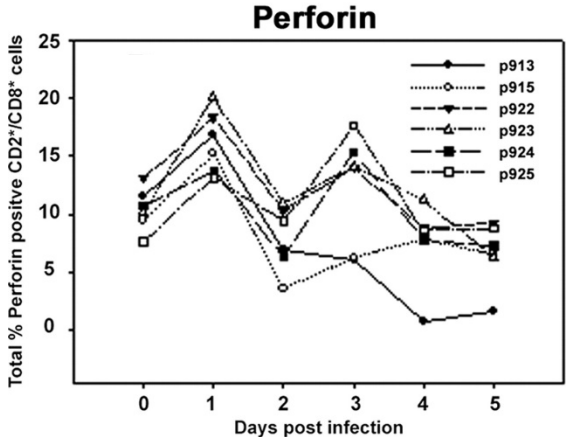
During pre-viremic and viremic stage of infection:

1. NK-dependent cytotoxic activity against target cells infected with FMDV is inhibited
2. The proportion of NK cells capable of producing gamma interferon and storing perforin was reduced









- No productive NK cell infection.
- Indirect effect of L^{pro} was proposed as possible mechanism.

Toka et al. 2009

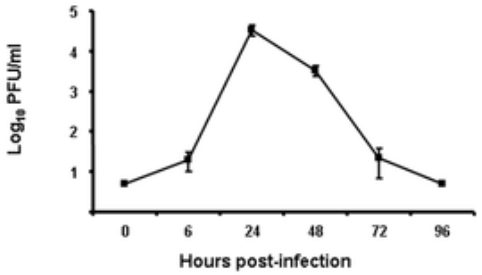
FMDV infects *ex vivo* matured moDCs

Infection is productive in immature CD172^{+} cells but abortive in moDCs

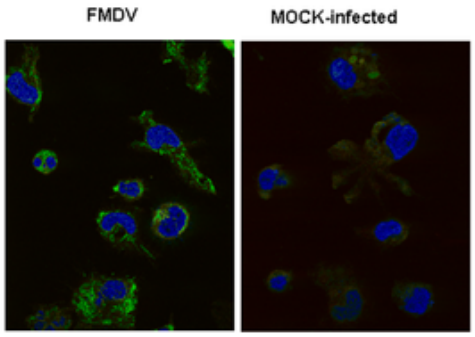
Infection affects maturation progression of moDCs:

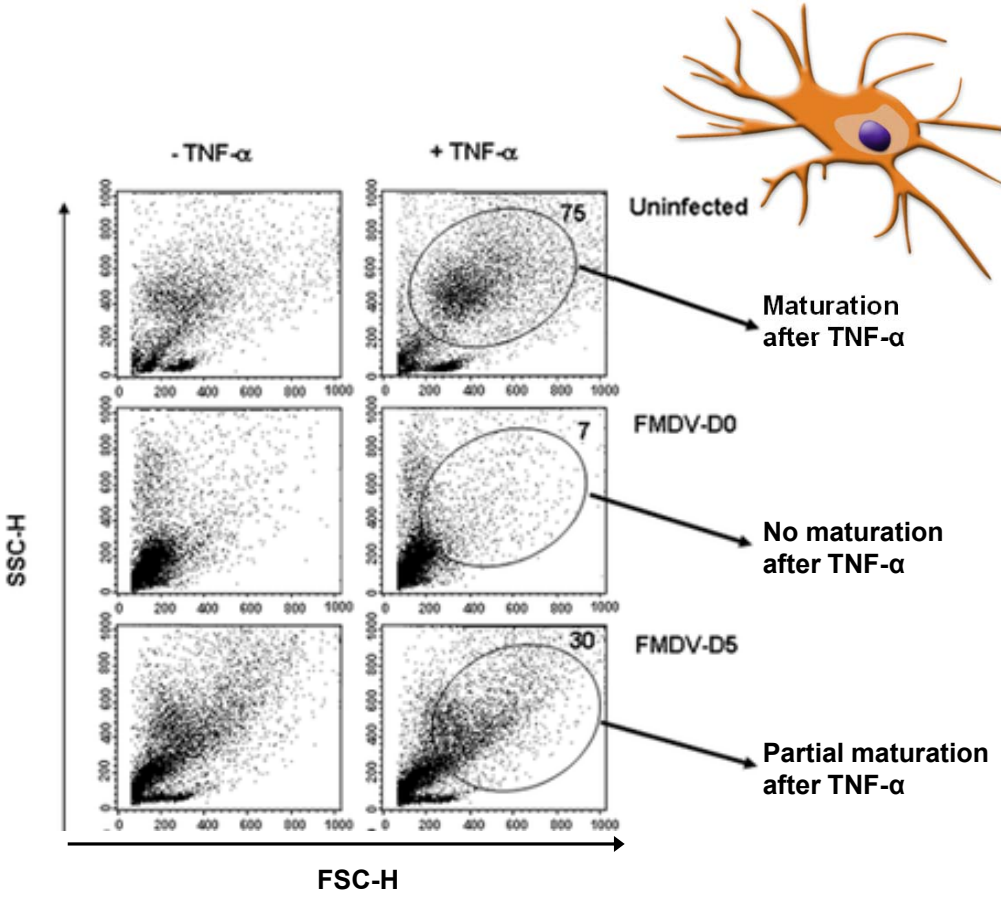
- ✓ SLA-II expression is affected.

CD172^{+} cells D0 maturation process:



CD172^{+} cells D5 maturation process:





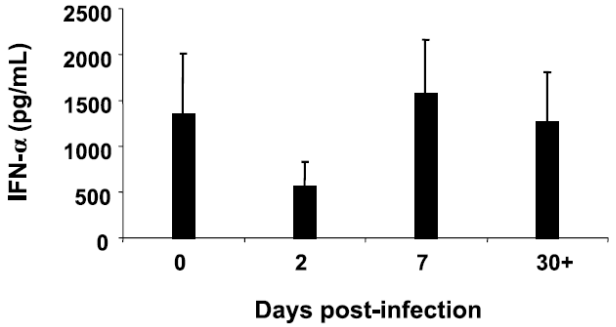
Diaz-San Segundo et al. 2009

FMDV infection suppresses IFN-α production

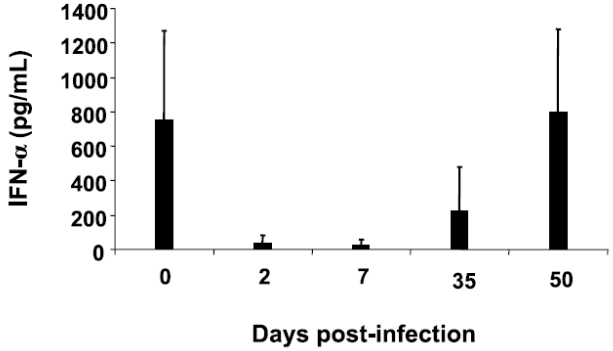
In vivo infection affects several DCs population:

- ✓ moDCs from infected animals do not produce IFN-α in response to *ex vivo* stimulation.
- ✓ Skin DCs from infected animals do not produce IFN-α in response to *ex vivo* stimulation.
- ✓ pDCs from infected animals decrease in number and do not produce IFN-α in response to *ex vivo* stimulation.

***Ex vivo* stimulated moDCs:**

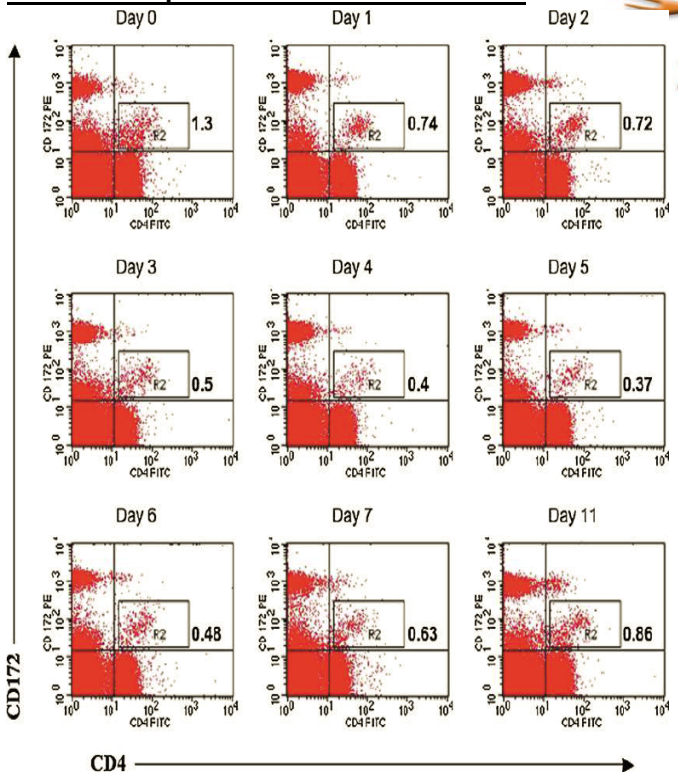


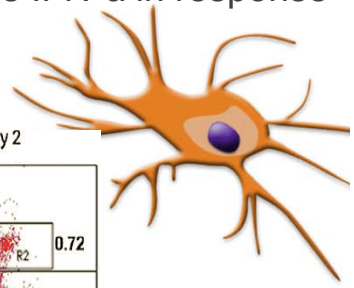
***Ex vivo* stimulated skin DCs:**



Nfon et al. 2008

Decrease of pDCs from infected animals:



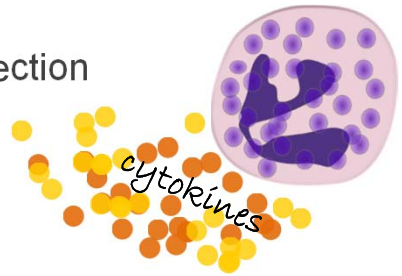


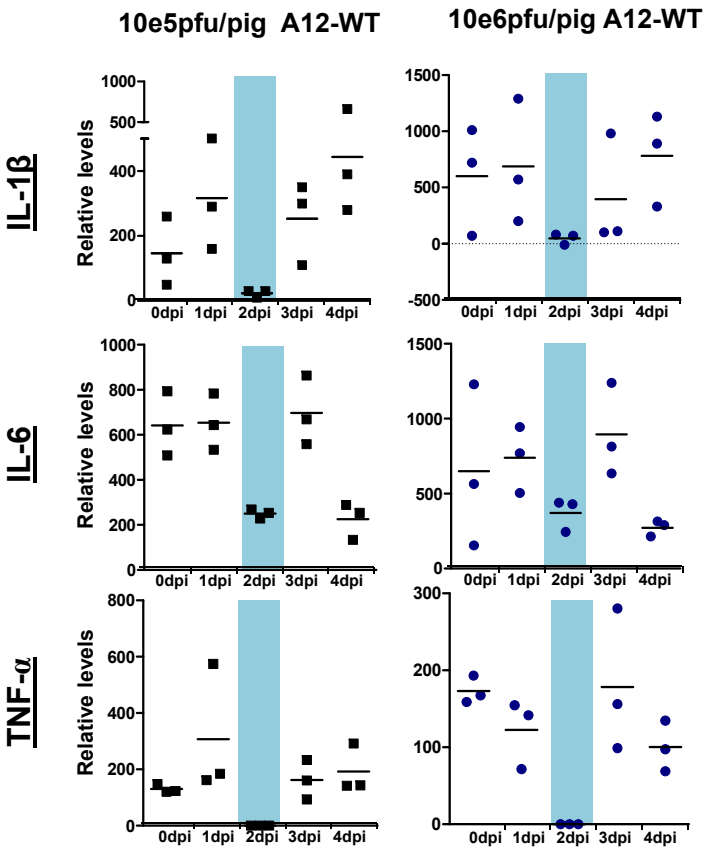
Nfon et al. 2010

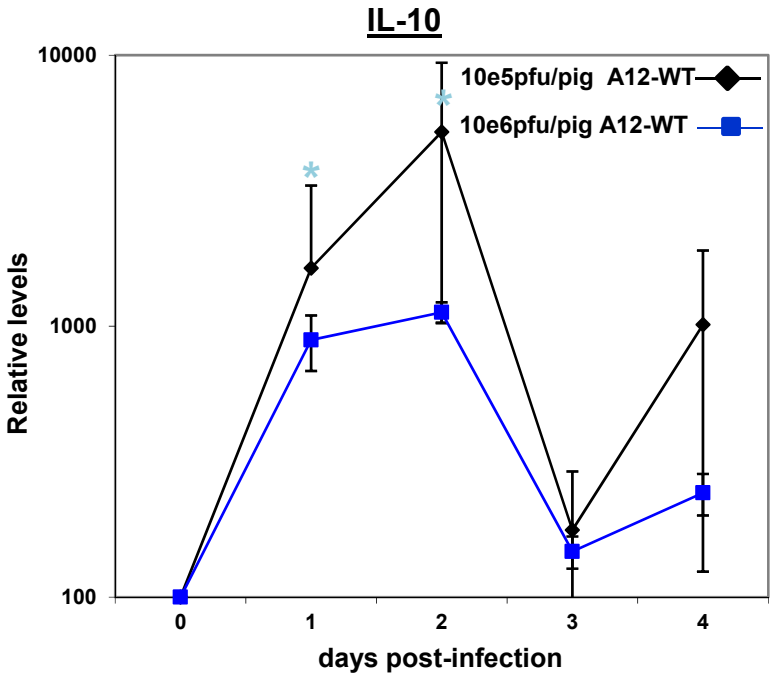
FMDV infection decreases systemic pro-inflammatory cytokines

IL-1β. IL-6 and TNF-α are significantly decreased

- ✓ Anti-inflammatory IL-10 is significantly increase during infection







Transcriptome analysis during FMDV infection

Type I IFN is no upregulated during pre-viremic phase.

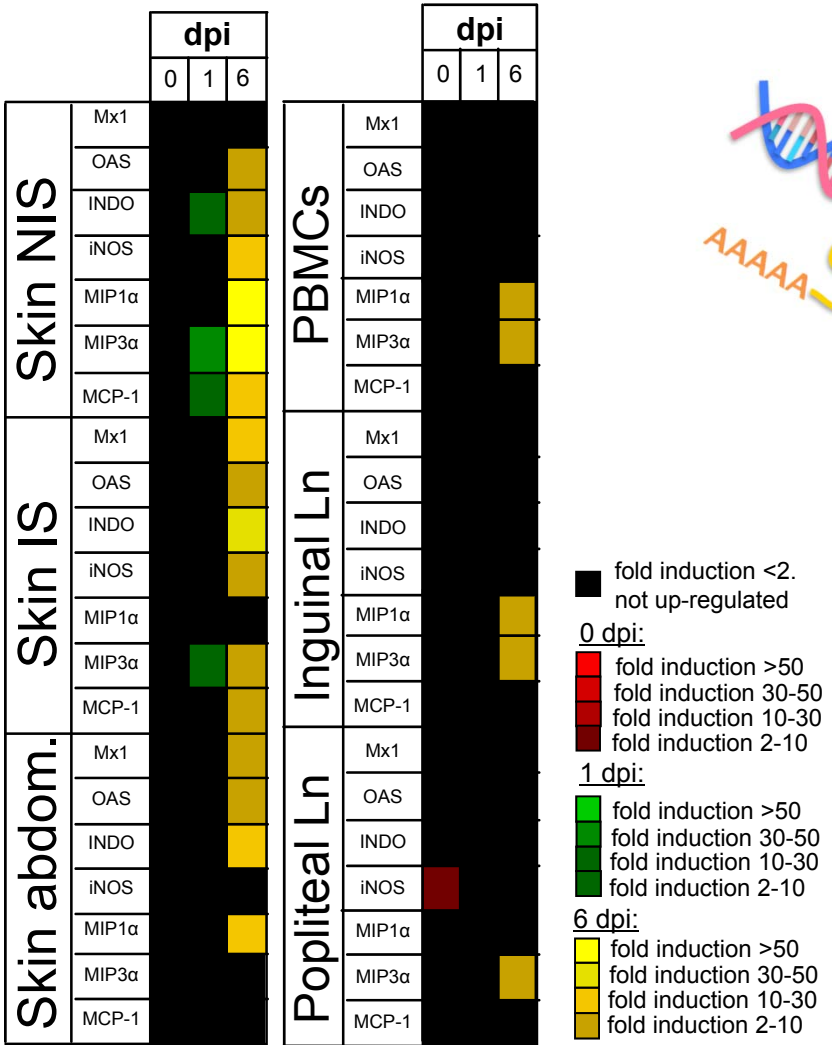
- ✓ IFN-β is up-regulated at later time-points.

IFN-β	0 dpi	1 dpi	6 dpi
Skin IS	0.85±2.28	1.94±3.8	34.5±3.25
Skin NIS	0.77±0.18	0.25±0.78	72±56.6
Skin Abdom.	0.59±0.33	0.3±0.45	3.58±0.25
PBMCs	0.03±0.03	1.94±0.38	2.09±1.59
IngLn	0.01±0.01	0.01±0.01	5.25±4.25
PopLn	1.2±3.4	0.24±0.3	4.2±3.4

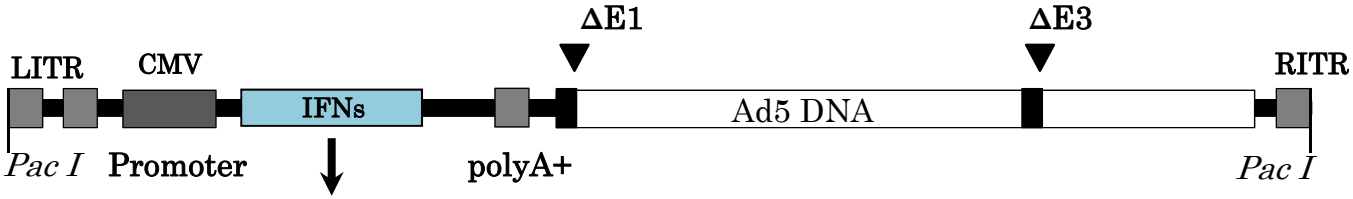
Transcriptome analysis during FMDV infection

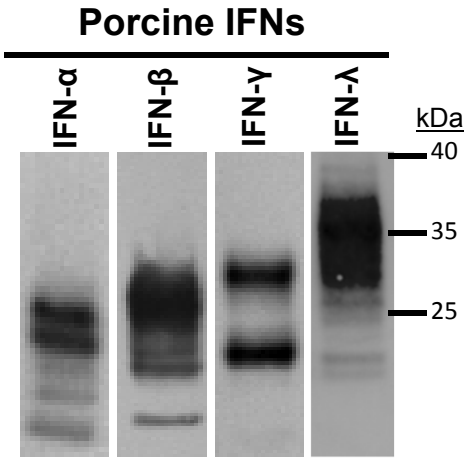
ISGs are barely up-regulated during pre-viremic phase.

- ✓ Six days after infection skin shows upregulation of several ISGs.

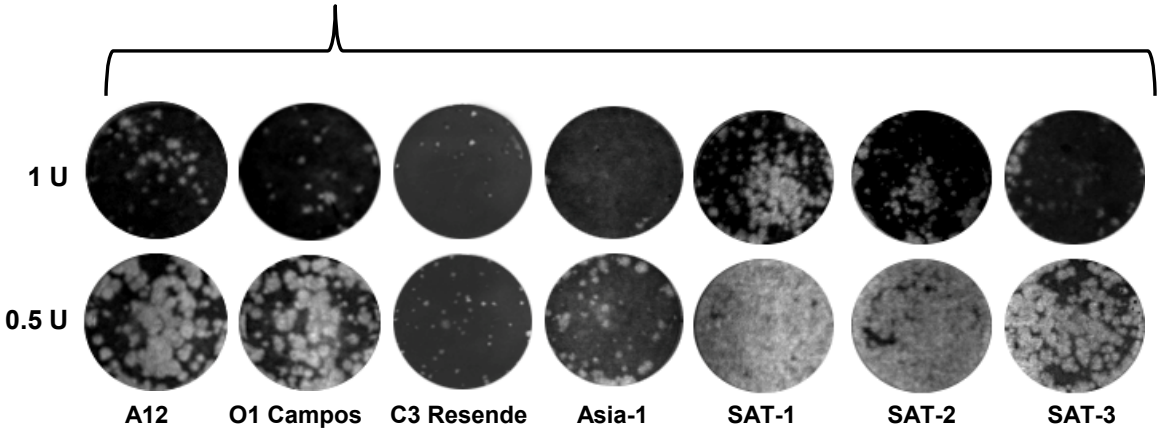


In vivo IFN treatment blocks FMDV replication and spreading





- ✓ Type I IFN: Chinsagaram et al., 2003; Moraes et al., 2003; Dias et al., 2011.
- ✓ Type II IFN: Moraes et al., 2007; Kim et al., 2014.
- ✓ Type III IFN: Perez-Martin et al., 2014

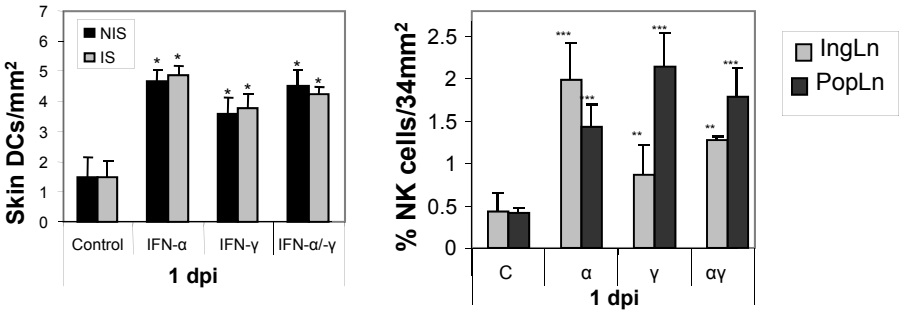


Diaz-San Segundo et al. 2017

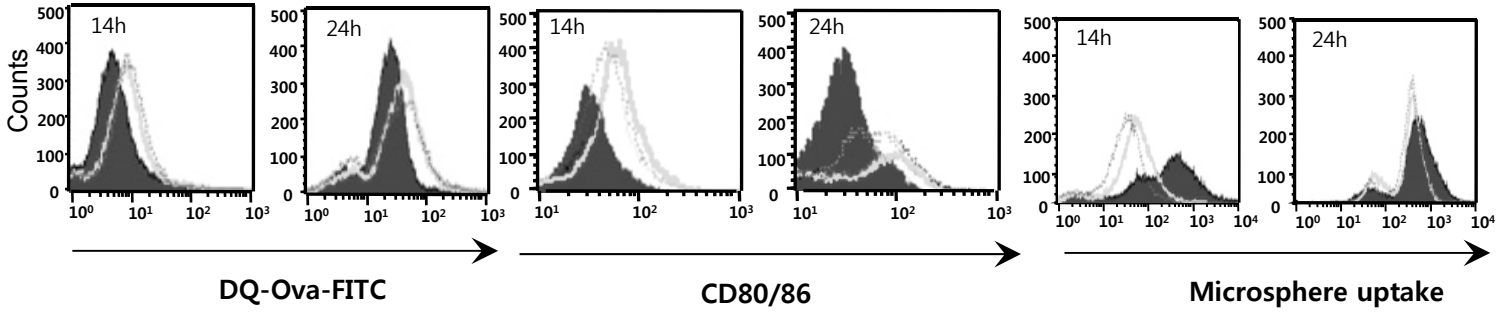
In vivo IFN treatment blocks FMDV replication and spreading

Protection correlates with stimulation of innate immune response.

- ✓ IFN induces recruitment of skin DCs and NK cells.



- ✓ IFN induces maturation of skin DCs.



- ✓ IFN induces local mRNA up-regulation of IFN and several ISGs.

Diaz-San Segundo et al. 2010; 2013

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