



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

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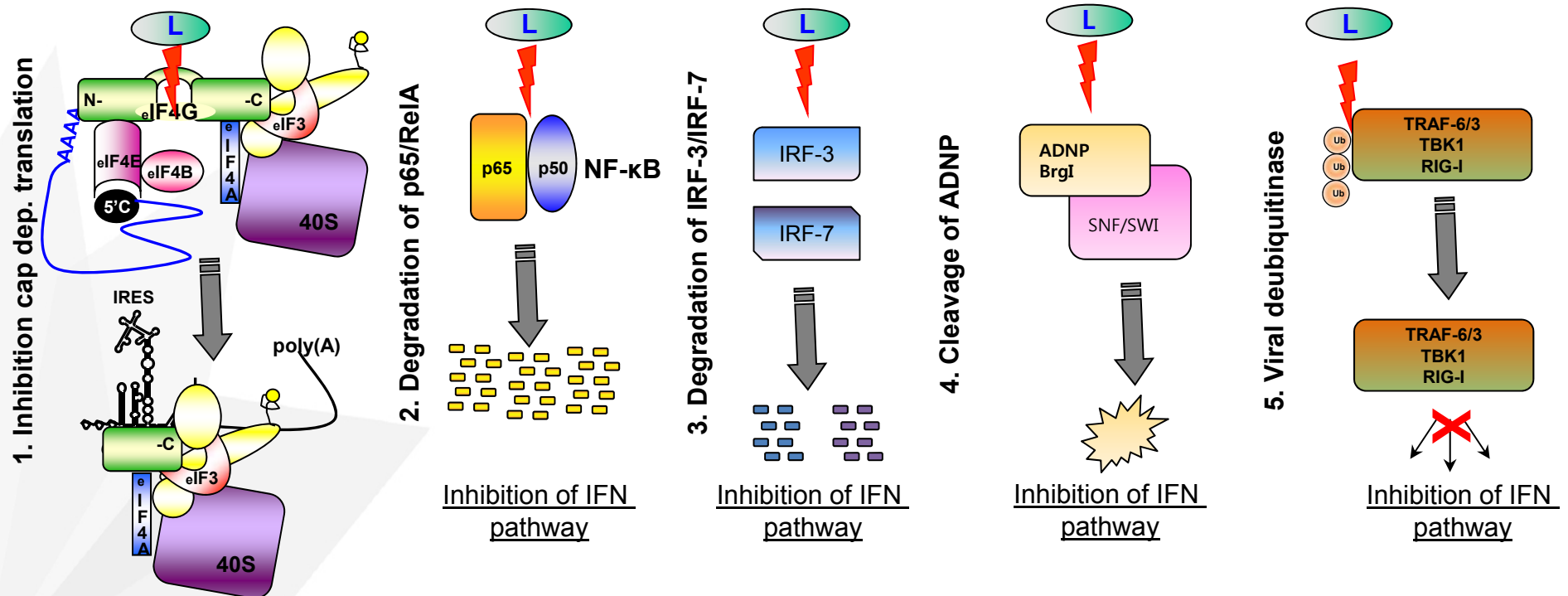
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FMDV controls cellular innate response



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

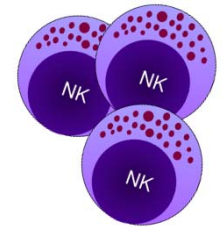
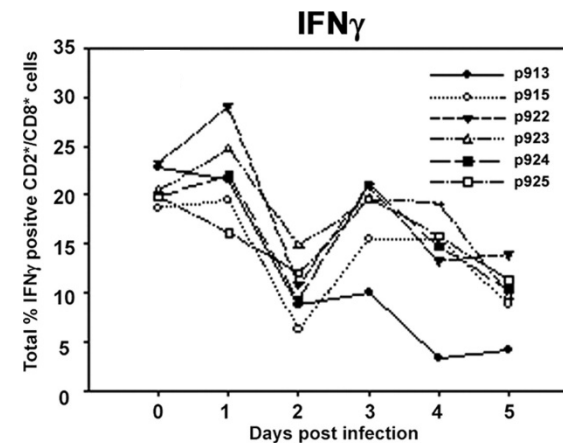
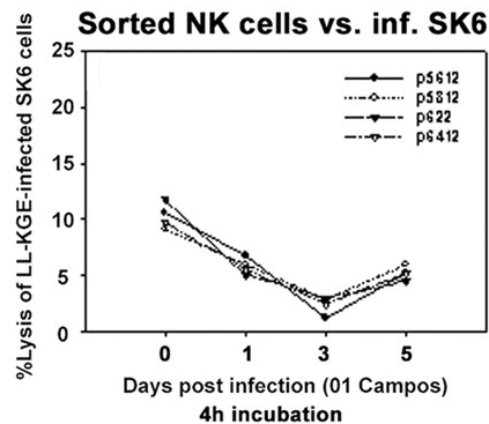
Medina et al, 2017

Wang et al.. 2011

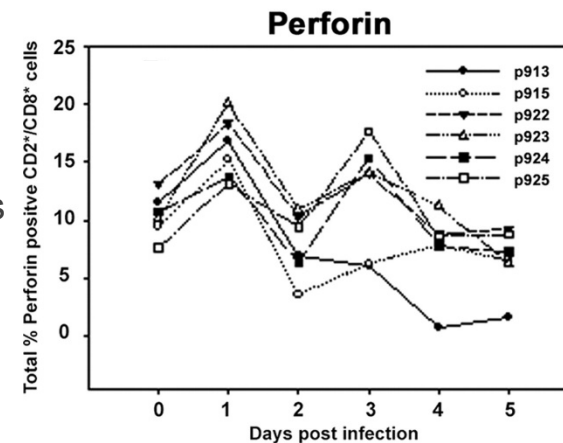
FMDV impairs NK cell lytic activity

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.



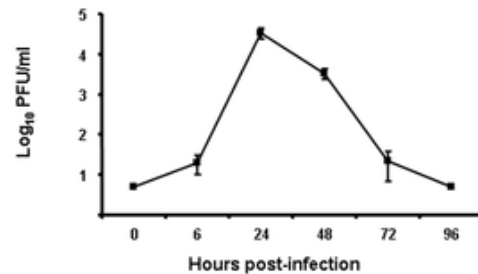
FMDV infects *ex vivo* matured moDCs

Infection is productive in immature CD172⁺ cells but **abortive** in moDCs

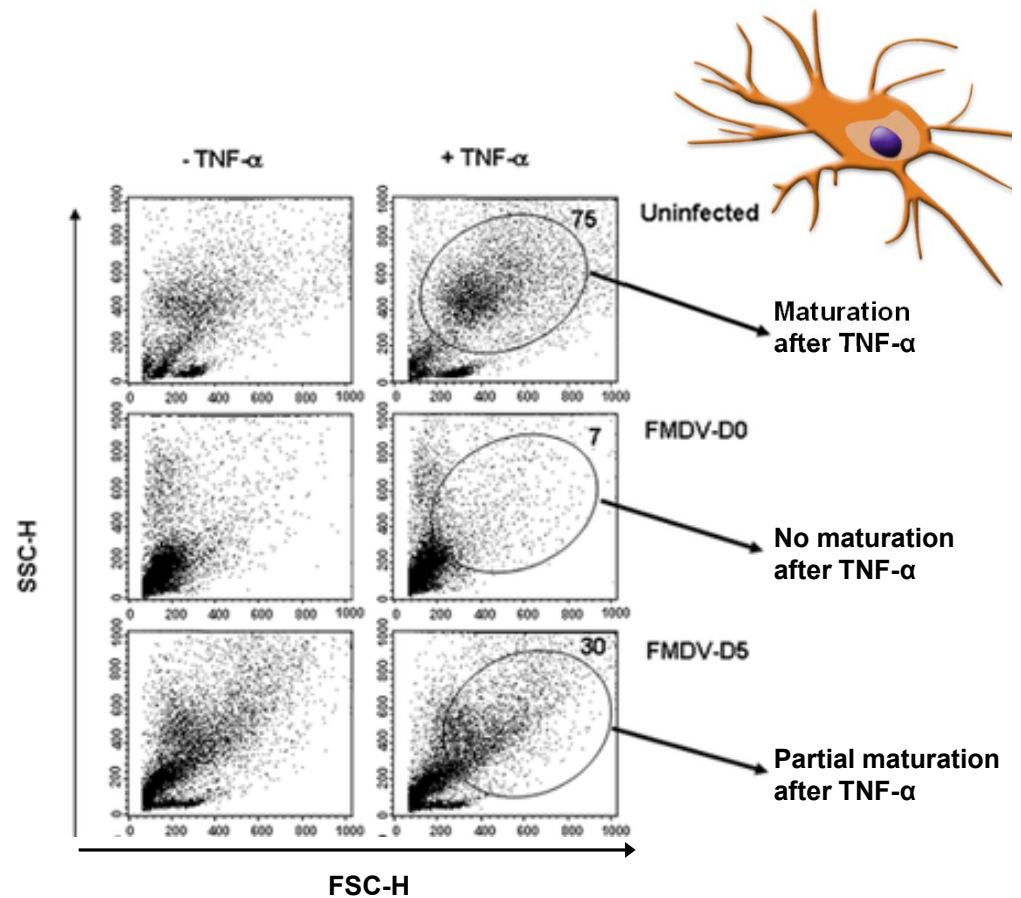
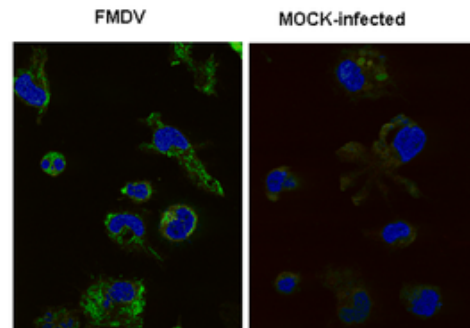
Infection affects maturation progression of moDCs:

- ✓ SLA-II expression is affected.

CD172⁺ cells D0 maturation process:



CD172⁺ cells D5 maturation process:

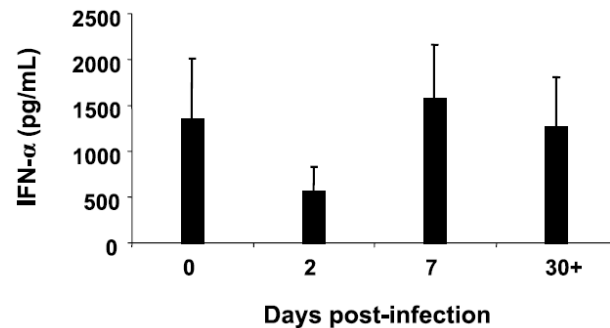


FMDV infection suppresses IFN- α production

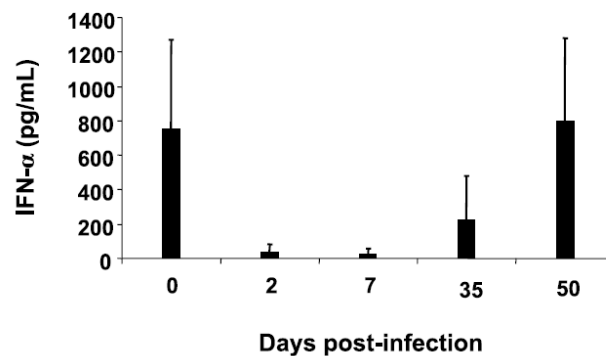
In vivo infection affects several DCs population:

- ✓ 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.

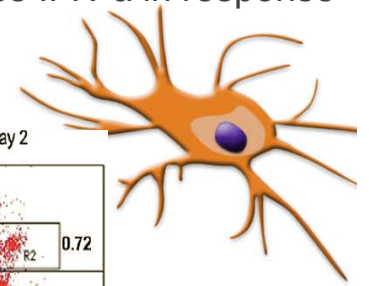
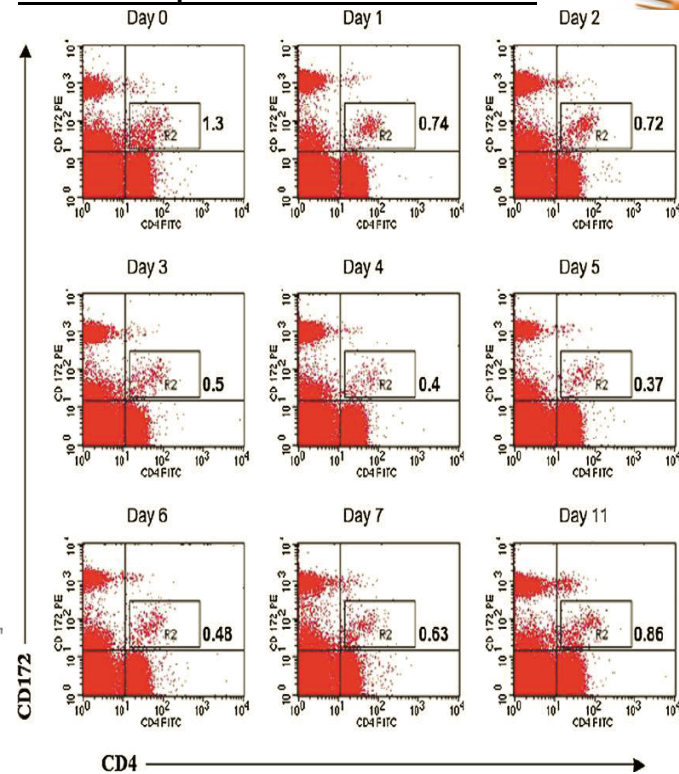
Ex vivo stimulated moDCs:



Ex vivo stimulated skin DCs:



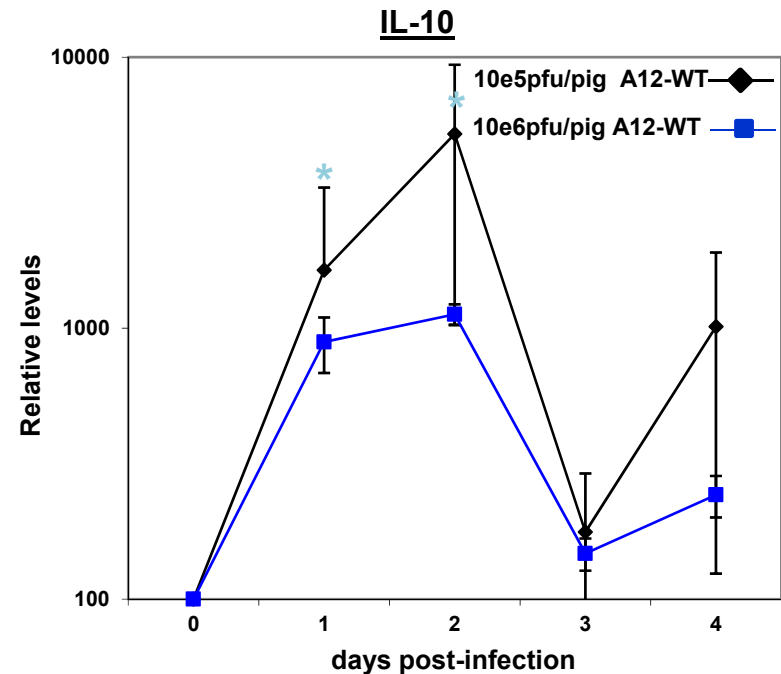
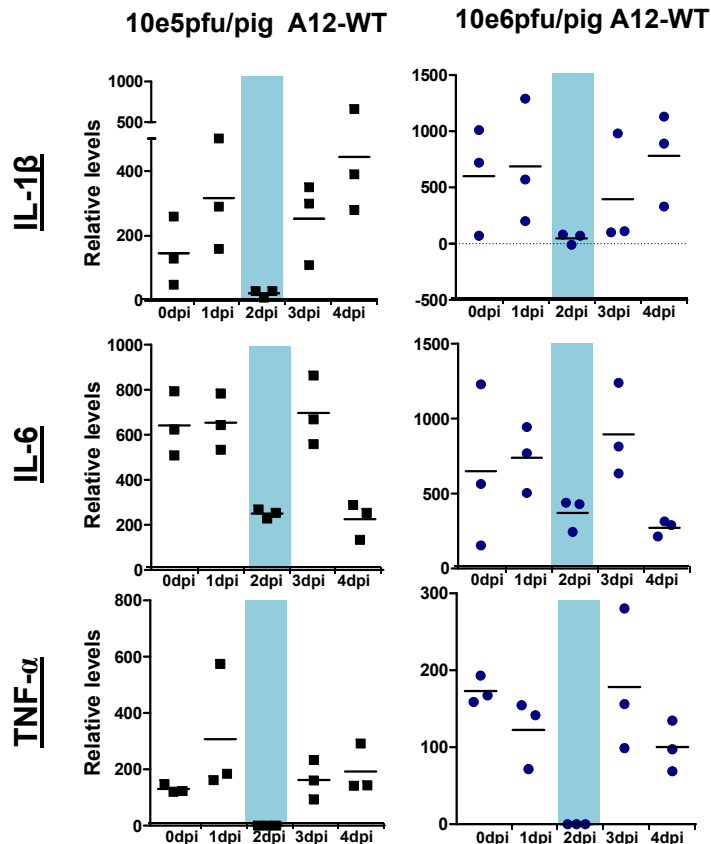
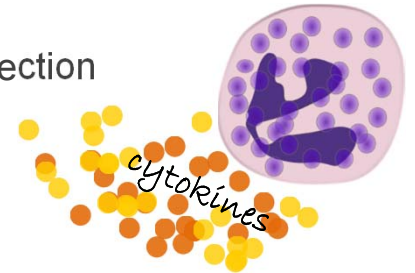
Decrease of pDCs from infected animals:



FMDV infection decreases systemic pro-inflammatory cytokines

IL-1 β , 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 not upregulated during pre-viremic phase.

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

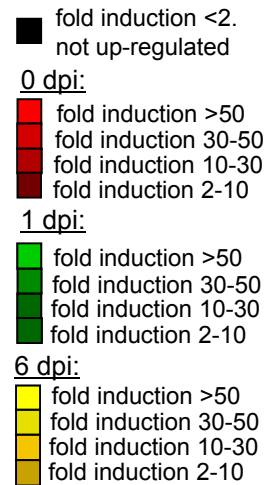
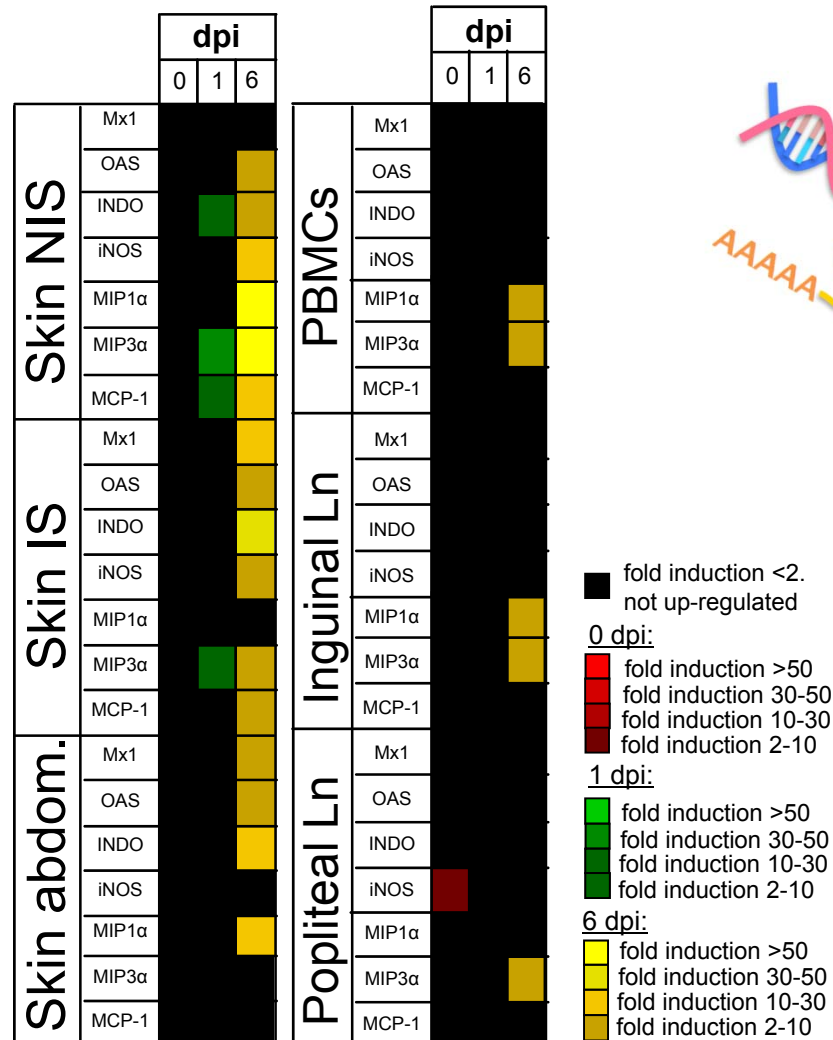
<u>IFN-β</u>	0 dpi	1 dpi	6 dpi
Skin IS	0.85 \pm 2.28	1.94 \pm 3.8	34.5 \pm 3.25
Skin NIS	0.77 \pm 0.18	0.25 \pm 0.78	72 \pm 56.6
Skin Abdom.	0.59 \pm 0.33	0.3 \pm 0.45	3.58 \pm 0.25
PBMCs	0.03 \pm 0.03	1.94 \pm 0.38	2.09 \pm 1.59
IngLn	0.01 \pm 0.01	0.01 \pm 0.01	5.25 \pm 4.25
PopLn	1.2 \pm 3.4	0.24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



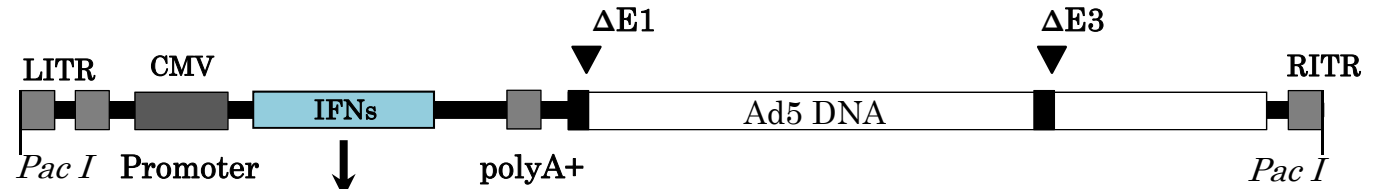
Transcriptome analysis during FMDV infection

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

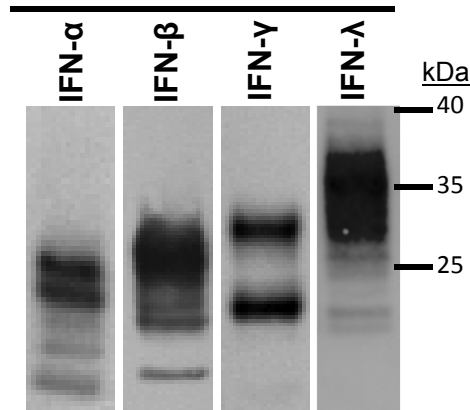
- ✓ Six days after infection skin shows upregulation of several ISGs.



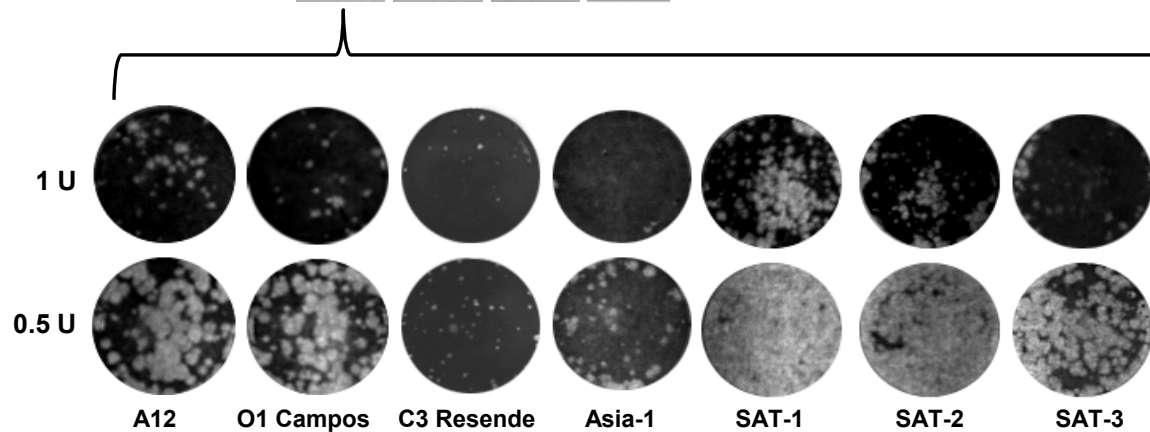
In vivo IFN treatment blocks FMDV replication and spreading



Porcine IFNs



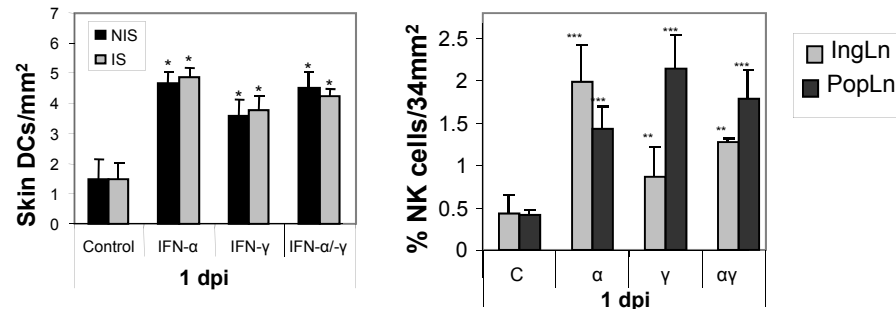
- ✓ Type I IFN: Chinsagaram et al., 2003; Moraes et al., 2003; Dias et al., 2011.
- ✓ Type II IFN: Moraes et al., 2007; Kim et al., 2014.
- ✓ Type III IFN: Perez-Martin et al., 2014



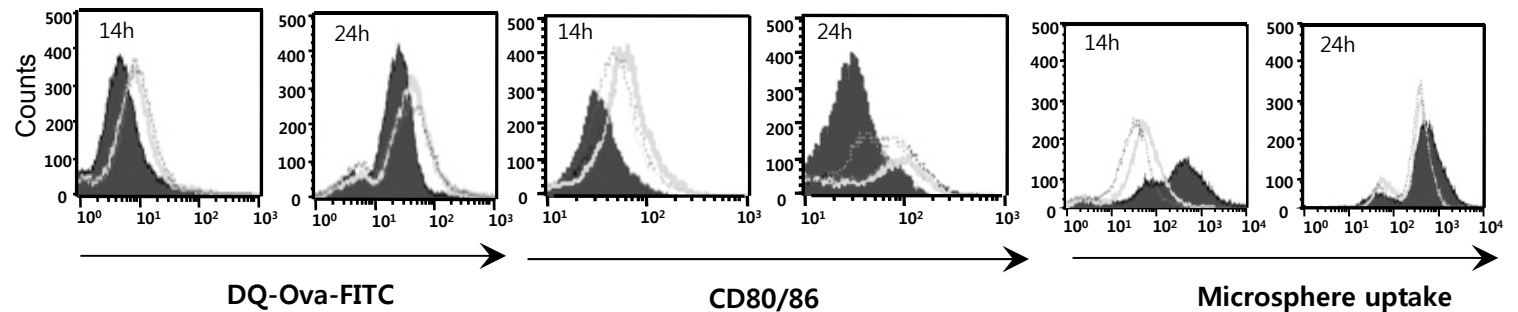
In vivo IFN treatment blocks FMDV replication and spreading

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.



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