

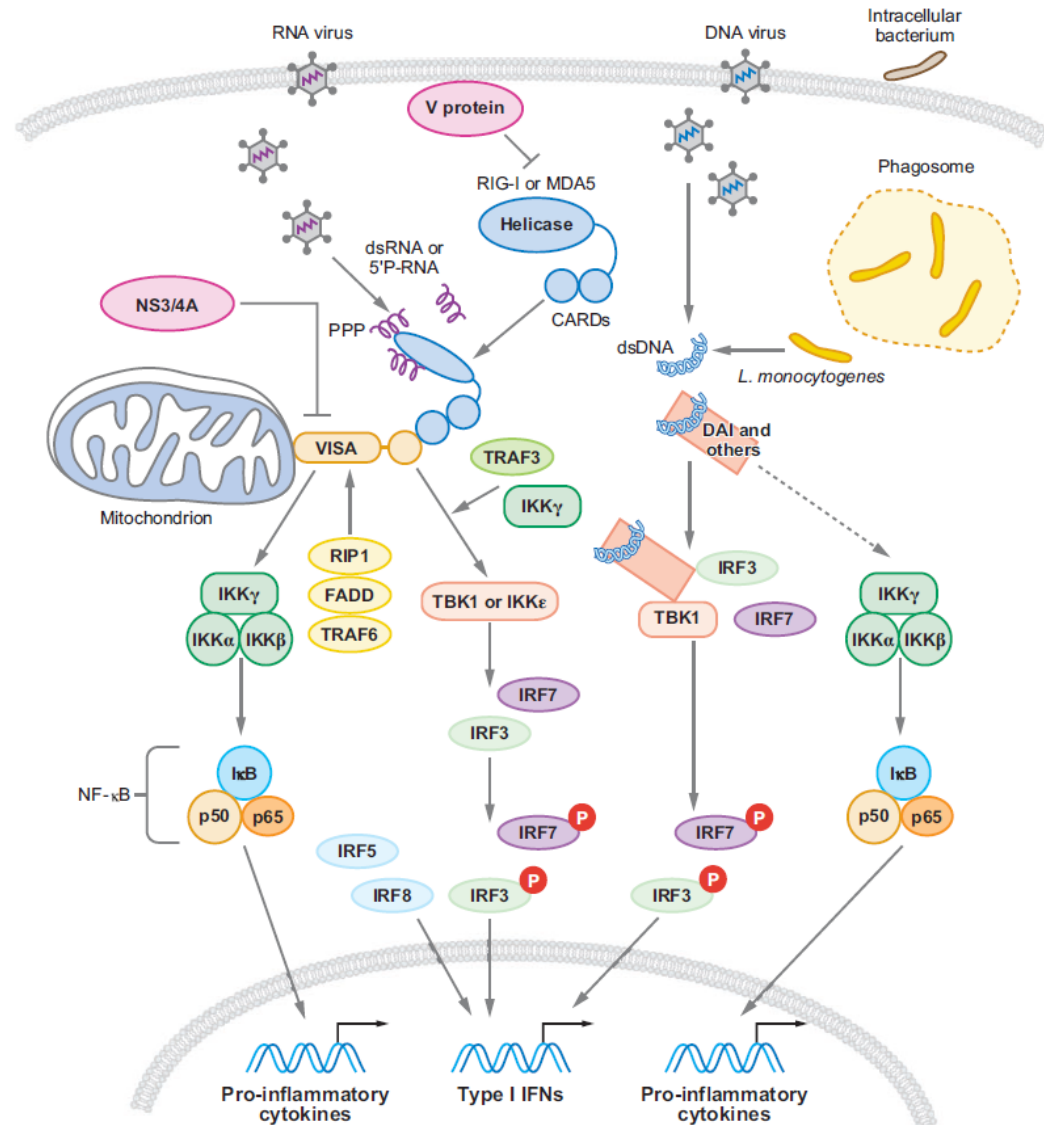
Идентификация и математическое моделирование
новых регуляторных контуров, балансирующих
противовирусные и воспалительные реакции

Identification and mathematical modeling of novel
regulatory circuits that balance antiviral and
inflammatory responses

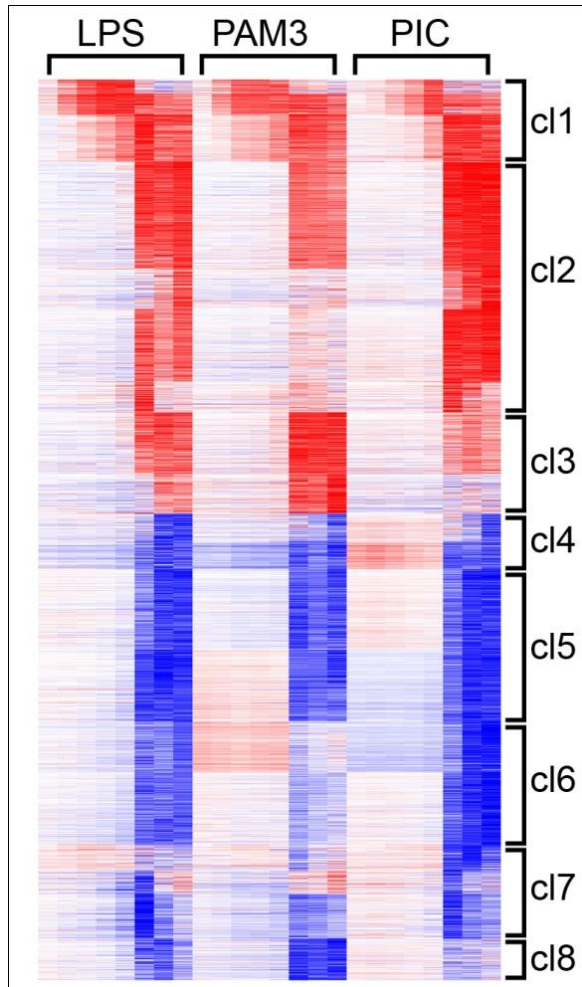
Александр Ратушный
Alexander Ratushny

Regulation of antiviral responses

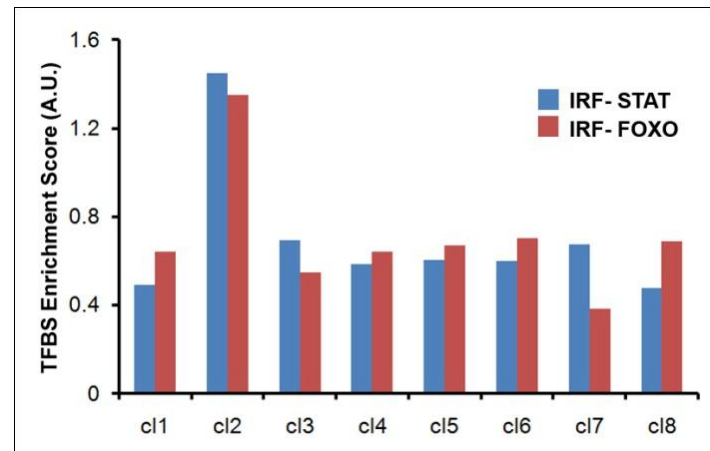
- Antiviral responses must be tightly regulated to rapidly defend against infection while minimizing inflammatory damage.
- Type 1 interferons (IFN-I) are crucial mediators of antiviral responses.
- Their transcription is regulated by a variety of transcription factors.
- Principal amongst these TFs is the family of interferon regulatory factors (IRFs).



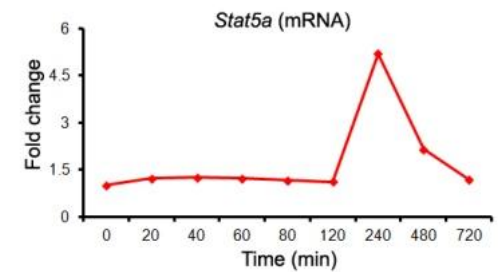
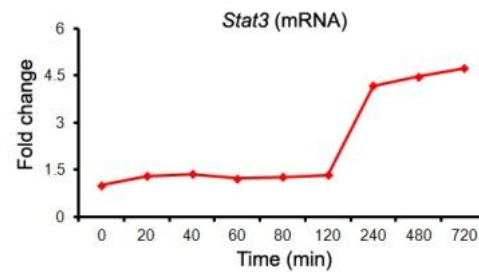
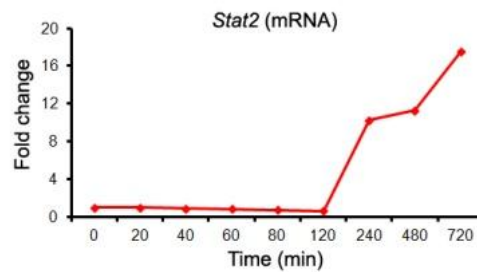
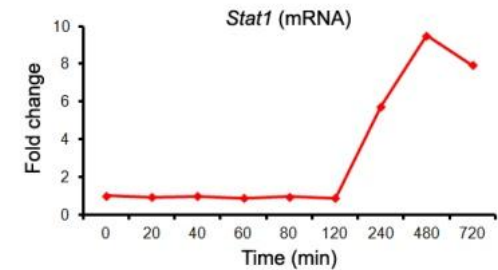
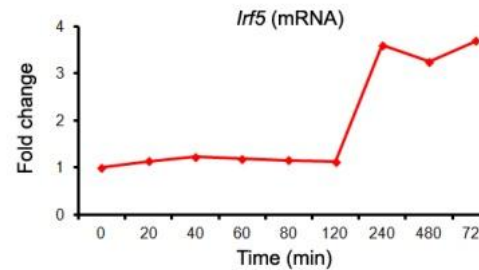
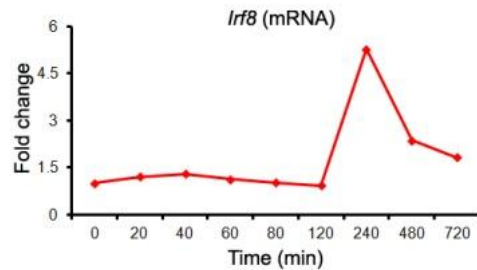
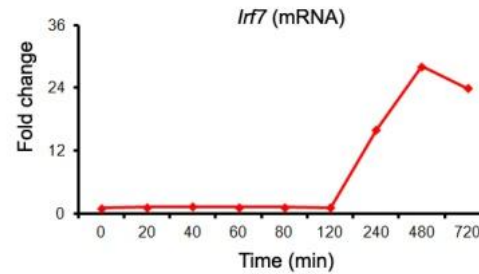
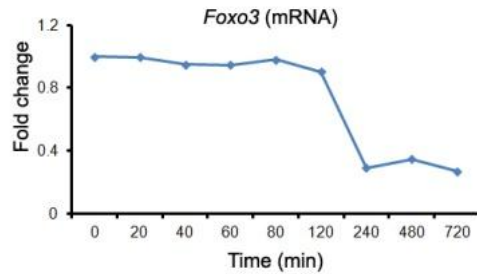
Gene expression and TFBS motif analysis



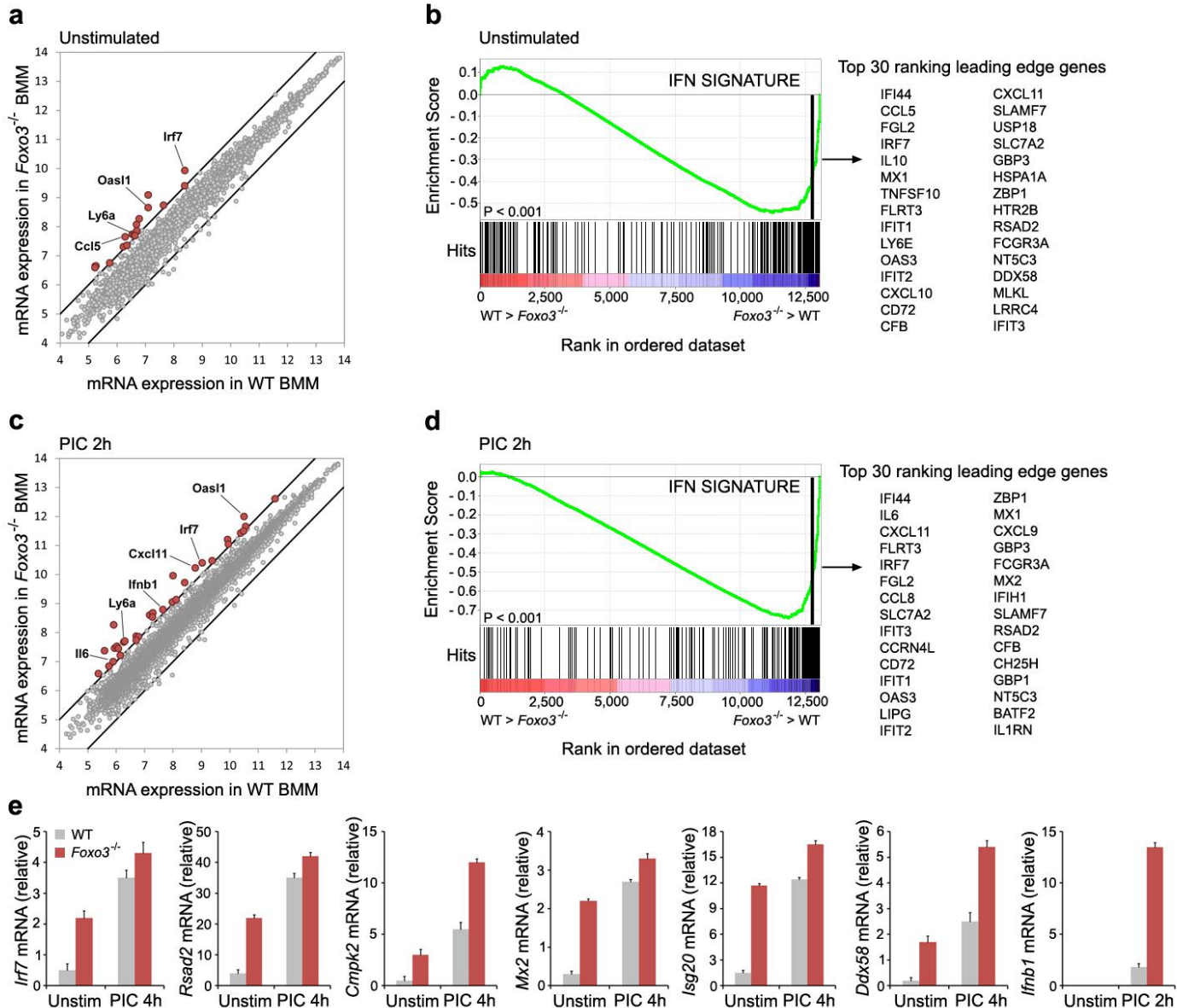
cl2 is a cluster of PIC/LPS induced genes that includes antiviral genes like *Gbp2*, *Ccl5*, *Ifit1*, *Irf7* and *Oasl1*



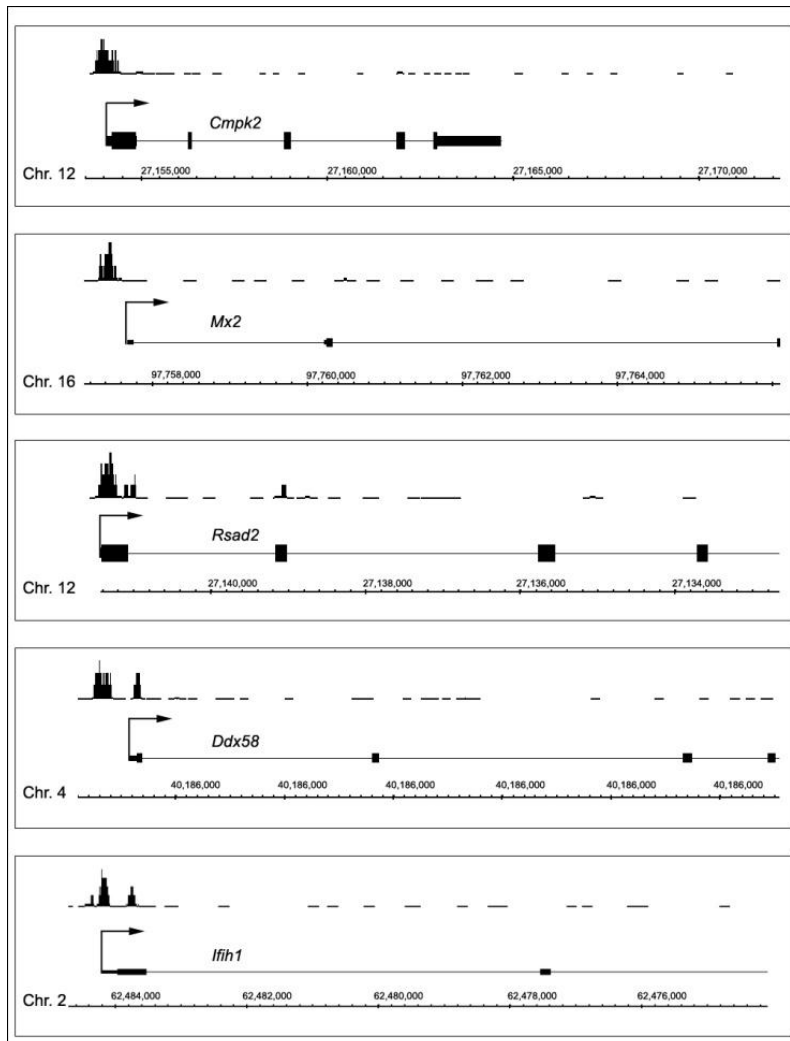
Transcription of PIC-induced and PIC-repressed TFs



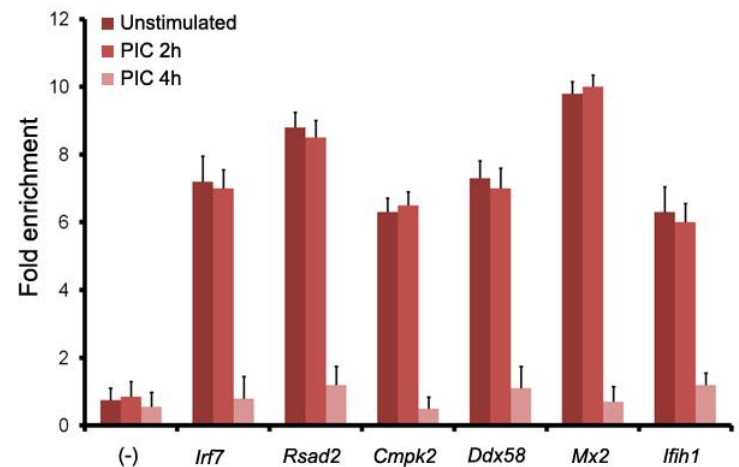
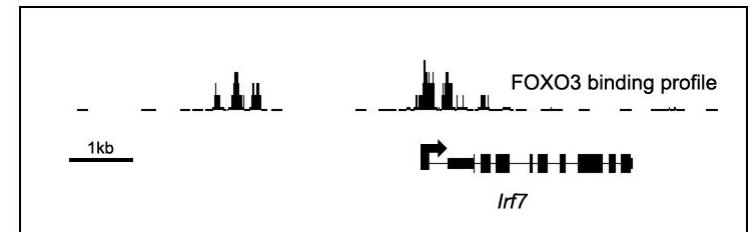
FOXO3 is a negative regulator of the antiviral response



FOXO3 directly binds the promoters of antiviral genes

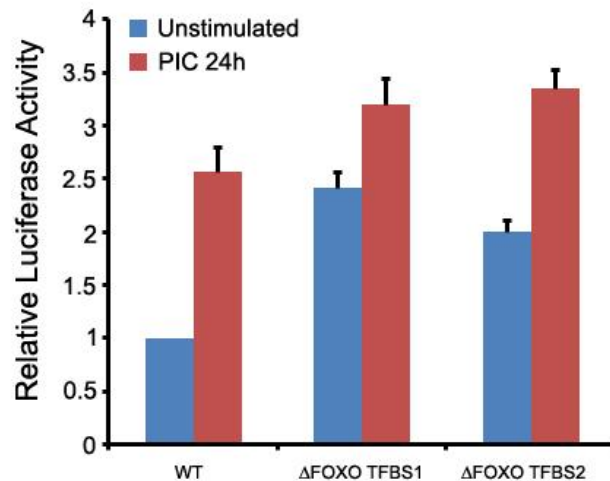


ChIP-Seq



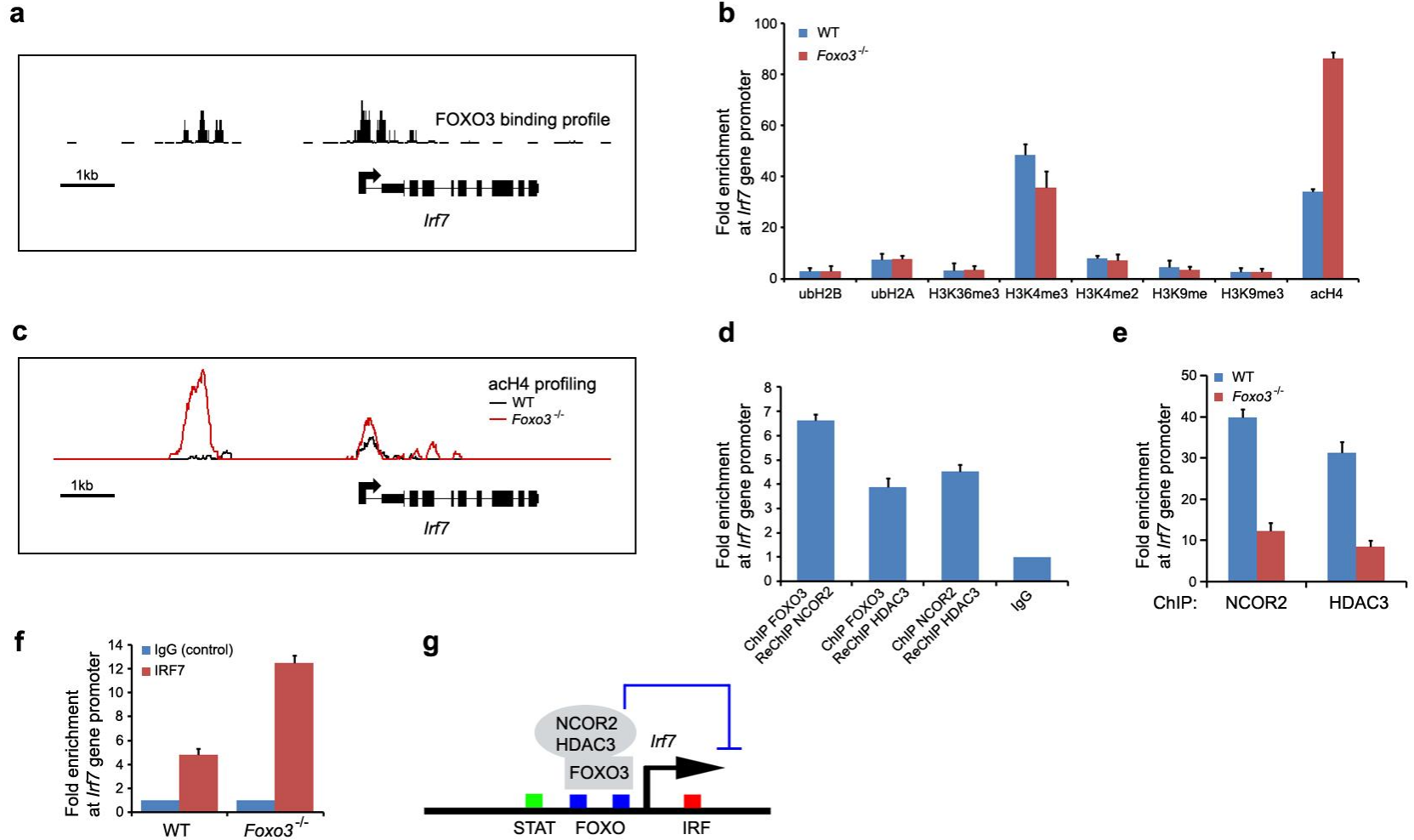
ChIP

FOXO TFBS in the *lrf7* gene promoter

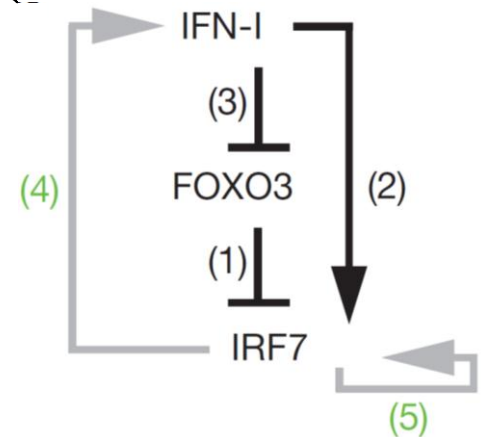
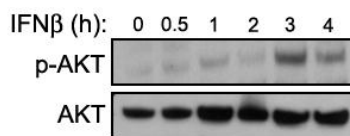
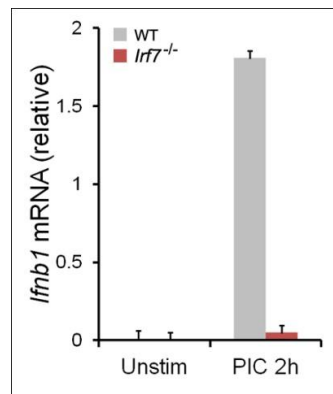
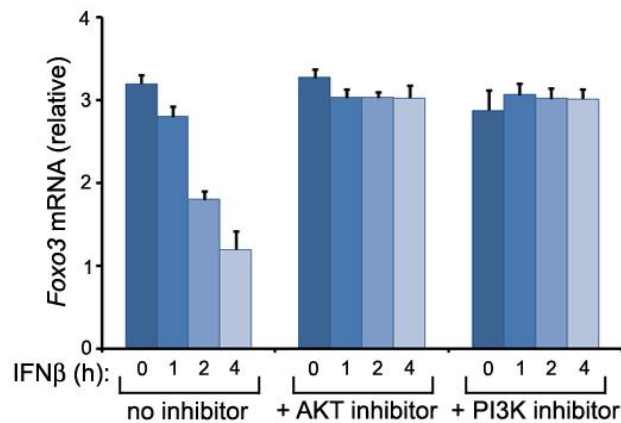
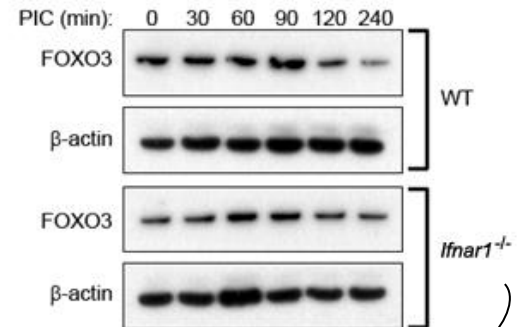
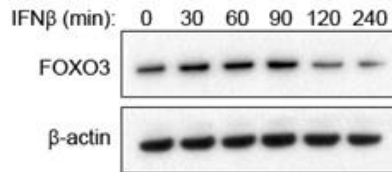
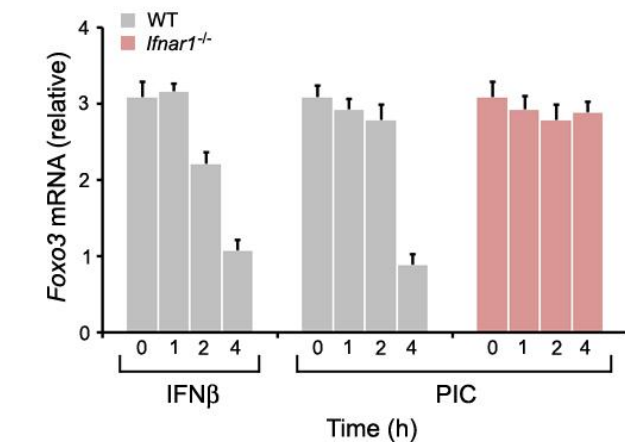
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Deletion of FOXO TFBS in the *Irf7* gene promoter resulted in an increased basal *Irf7* promoter activity

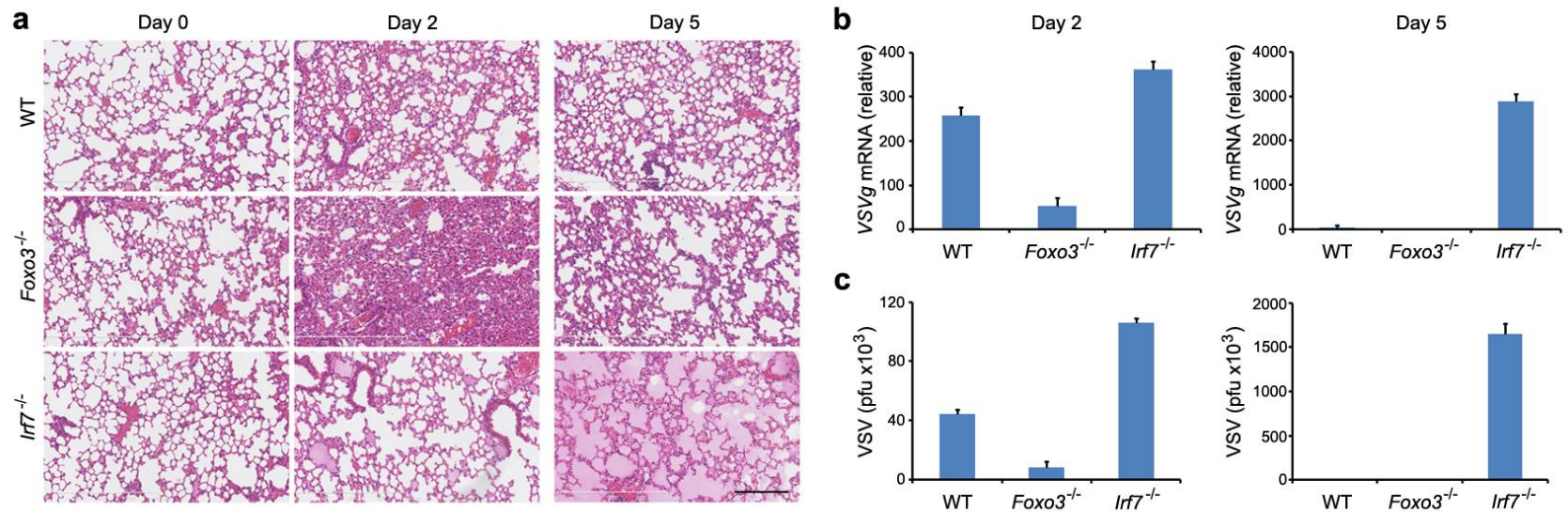
FOXO3 keeps the *Irf7* gene in check



FOXO3/IRF7/IFN-I regulatory circuit

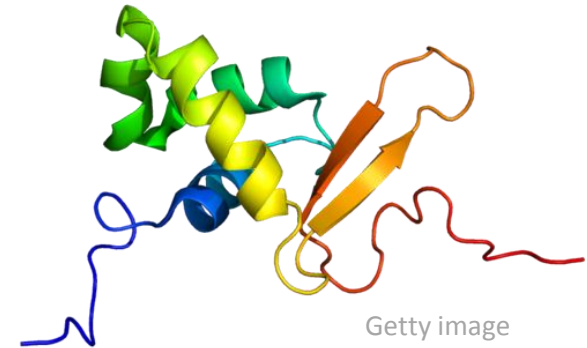


Antiviral responses lead to increased lung injury in the absence of FOXO3 and IRF7



Role of FOXO3 in the regulation of antiviral responses

- FOXO3 is a negative regulator of a subset of antiviral genes.
- Genome-wide location analysis combined with gene deletion studies identified the *Irf7* gene as a critical target of FOXO3.
- FOXO3 was identified as a negative regulator of *Irf7* transcription
- FOXO3/IRF7/IFN-I regulatory circuit represents a novel mechanism that balances the beneficial effects and deleterious sequelae of the antiviral response.



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