Secreted INFβ Coordinates Antiviral Response

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***Short Abstract* — Virus-infected or poly(I:C)-stimulated cells secrete IFNβ, which coordinates population antiviral responses. By combining experiments and our mathematical model of the NF-κB–IRF3–STAT1/2 signalling network, we show that IFNβ priming increases apoptosis in MEFs responding to poly(I:C) by initiating activation of STAT1/2, which in turn induces expression of antiviral components, RIG-I, PKR and OAS1A.**

I. Background

PROGRAMMED cell death, or apoptosis, is a key cellular mechanism protecting against the spread of viral infection. Virus-infected cells can activate transcription factors NF-κB and IRF3, both of which are required for the production of IFNβ. A cell receiving secreted IFNβ responds by activation of transcription factor STAT1/2 and consequent upregulation of its antiviral components. Among them are RIG-I, cytosolic receptor for viral dsRNA, PKR, inhibitor of translation, and OAS1A, functioning in mRNA degradation. Using experiments and our stochastic model of the NF-κB–IRF3–STAT1/2 signalling network (Fig. 1), we elucidate how IFNβ coordinates population antiviral responses to poly(I:C), an analog of viral dsRNA.

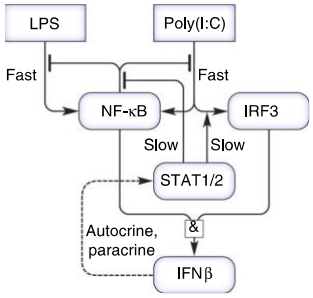

Fig. 1. Simplified diagram of the mathematical model of the NF-κB–IRF3–STAT1/2 signalling network.

II. Results

Priming MEF cells with IFNβ on its own does not activate NF-κB or IRF3 and does not cause apoptosis (Fig. 2). Stimulation of these cells with poly(I:C) transiently activates NF-κB and/or IRF3 and causes apoptosis in approximately 25% of the population.

IFNβ priming followed by stimulation with poly(I:C) increases the fraction of cells that activate both NF-κB and IRF3, prolongs this activity, and increases the fraction of apoptotic cells over three-fold, compared to stimulation with poly(I:C) alone (Fig. 2).

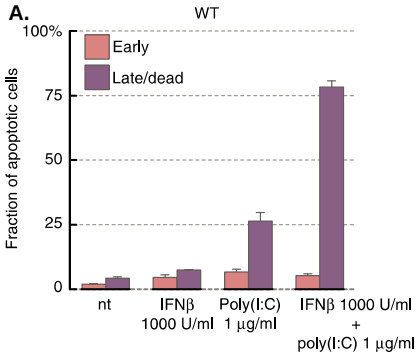

Fig. 2. Effect of INFβ priming on responses to poly(I:C) in WT MEFs.

In addition, IFNβ priming in MEF *Stat1*$^{-/-}$ cells has no effect on the activation of NF-κB and/or IRF3 in response to poly(I:C), and no effect on the fraction of apoptotic cells, compared to stimulation with poly(I:C) alone [1]. Activation of NF-κB and/or IRF3 in response to poly(I:C) alone occurs in fraction of MEF *Stat1*$^{-/-}$ cells smaller than in WT MEFs [1].

III. Conclusion

IFNβ priming sensitises naïve cells to poly(I:C) through expression of STAT1/2-dependent genes, such as RIG-I, PKR and OAS1A. When subsequently activated by poly(I:C), their protein products override the negative feedbacks on NF-κB and initiate a positive feedforward to IRF3 (Fig. 1). As a result of prolonged activity of NF-κB and IRF3, more cells commit to apoptosis, thus limiting infection spread.

References

[1] Czerkies M, *et al.* (2018) Cell fate in antiviral response arises in the crosstalk of IRF, NF-κB and JAK/STAT pathways, *Nat Commun*. **9**, 493.

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