Nature Reviews Immunology | Published online 14 December 2015; doi:10.1038/nri.2015.14

S. Bradbrook/NPG

INNATE IMMUNITY

First aid at the epithelium

The induction of interferons (IFNs) is believed to represent a first line of immune defence against viruses. Paludan and colleagues now describe a novel innate pathway that provides antiviral protection at epithelial surfaces before IFNs are induced. Intriguingly, this pathway does not involve any known innate sensors of viral infection but seems to be linked to disruption of the mucus layer.

Many viral pathogens infect the host via mucosal surfaces, and the authors were interested in exploring the innate immune mechanisms that protect epithelium. They infected mice intravaginally with herpes simplex virus 2 (HSV-2) and characterized viral loads and cytokine production at early time-points. Surprisingly, although viral replication and induction of the CXC-chemokine receptor 3 (CXCR3) ligands CXCL9 and CXCL10 were observed within 24 hours of HSV-2 infection, the upregulation of type I and type II IFNs did not occur until 48 hours. Similar findings were made in an ocular model of HSV-1 infection, suggesting that HSV infection induces the expression of CXCR3 ligands before the production of IFNs.

Experiments in CXCR3-deficient mice showed that the early induction of CXCL9 and CXCL10 is important for limiting viral replication. Compared with wild-type controls, CXCR3-deficient mice had higher viral loads at 24 hours, but not at 48 hours, after HSV-2 infection. By contrast, mice lacking the IFNα/β receptor had similar viral loads to wild-type mice at 24 hours post-infection, but showed increased viral burdens by 48 hours. Vaginal epithelial cells were found to be a major source of early CXCL10 production, and this correlated with activation of nuclear factor-κB in these cells at 24 hours post-infection. Interestingly, CXCL10 was also produced by epithelial cells that were not productively infected with HSV-2.

> “mammalian innate immune responses may be activated indirectly by the consequences of pathogen activity”

To identify the epithelial sensing mechanisms involved, the authors compared mouse strains that were deficient for pattern-recognition receptors (PRRs) or adaptor molecules associated with innate sensing of viruses. Strikingly, none of the deficient mice showed impairment of CXCL10 induction or increased viral loads at 24 hours after HSV infection. In addition, administration of mice with ultraviolet-inactivated HSV-2 or a mutant strain of HSV-2 that could not enter host cells still stimulated early CXCL10 production. Therefore, the authors examined the role of glycans that are exposed on the surface of HSV-2. They found that viruses lacking *N*-glycans still induced early CXCL10 production, but viruses lacking *O*-linked glycans or expressing truncated forms of these glycans could not induce this response.

Viral *O*-linked glycans did not stimulate early chemokine production by triggering C-type lectin receptors. Instead, experiments showing that CXCL10 is induced in response to mechanical or enzymatic disruption of the genital mucosa suggested that viral glycans induce a chemokine response by disrupting the integrity of the mucus layer. Indeed, HSV expressing truncated *O*-linked glycans could not establish replication foci in the vaginal epithelium at 24 hours following infection, suggesting that HSV-2 uses *O*-linked glycans to penetrate the mucus layer and establish infection. The early chemokine response induced by HSV-2 was shown to protect the host by inducing neutrophil recruitment, and the depletion of neutrophils at 24 hours post-infection led to more severe disease in HSV-2-infected mice.

In summary, the disruption of mucus integrity by HSV-2 seems to lead to an early chemokine-driven neutrophil response; the authors suggest that this may allow the host to eliminate infectious agents without inducing potentially pathological IFN responses. Although the signalling mechanisms involved are not known, the authors speculate that there could be disruption of an inter-mucin network. Therefore, in a similar manner to the ‘guard theory’ of plant immunity (see Further Reading), mammalian innate immune responses may be activated indirectly by the consequences of pathogen activity, as well as directly by PRR stimulation.

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ORIGINAL ARTICLE Iversen, M. B. *et al.* An innate antiviral pathway acting before interferons at epithelial surfaces. *Nat. Immunol.* http://dx.doi.org/10.1038/ni.33319 (2015)
FURTHER READING Spoel, S. H. & Dong, X. How do plants achieve immunity? Defence without specialized immune cells. *Nat. Rev. Immunol.* **12**, 89–100 (2012)