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**This is the author's manuscript**

*Original Citation:*

*Availability:*

This version is available http://hdl.handle.net/2318/1526695 since 2016-09-17T23:55:56Z

*Published version:*

DOI:10.1016/j.cyto.2015.08.220

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20 April 2024

**The nuclear Interferon-inducible IFI16 protein and the innate sensing to HPV18 replication**

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Intrinsic immunity is mediated by cellular restriction factors that are constitutively expressed and active even before a pathogen enters the cell. The host nuclear factor IFI16 acts as sensors of foreign DNA and antiviral restriction factors. It is a multifunctional nuclear protein involved in transcriptional regulation, induction of Interferon-β (IFN-β), and activation of the inflammasome response. It interacts with the sugar-phosphate backbone of dsDNA and modulates viral and cellular transcription through largely undetermined mechanisms. IFI16 is a restriction factor for Human Cytomegalovirus (HCMV) and Herpes Simplex virus (HSV-1). We have recently demonstrated that IFI16 has also a profound effect on HPV18 replication in human keratinocytes (NIKS cells transfected with religated HPV18 genome) and the osteosarcoma cell line U2OS, transfected by electroporation with HPV18 minicircles (Lo Cigno et al., J Virol 2015). ChIP studies demonstrated that IFI16 promotes the addition of heterochromatin marks and the reduction of euchromatin marks on viral chromatin at both early and late promoters, thus reducing both viral replication and transcription. Type I IFN response was not involved in the observed phenotypes. Experiments are underway with EdU-labelled HPV18 minicircles to visualize any interaction with IFI16 at the early stages of infection, and to clarify which molecular events regulate the IFI16 immune-sensing to HPV. Altogether, these results argue that IFI16 restricts chromatinised HPV DNA through epigenetic modifications and executes a broad surveillance role against viral DNA in the nucleus that is not restricted to Herpesviruses.