Viral enhancer mimicry of host innate-immune promoters

Citation for published version:
Kropp, KA, Angulo, A & Ghazal, P 2014, 'Viral enhancer mimicry of host innate-immune promoters', Plos Pathogens, vol. 10, no. 2, e1003804. https://doi.org/10.1371/journal.ppat.1003804

Digital Object Identifier (DOI):
10.1371/journal.ppat.1003804

Link:
Link to publication record in Edinburgh Research Explorer

Document Version:
Publisher's PDF, also known as Version of record

Published In:
Plos Pathogens

Publisher Rights Statement:
Copyright: © 2014 Kropp et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

General rights
Copyright for the publications made accessible via the Edinburgh Research Explorer is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy
The University of Edinburgh has made every reasonable effort to ensure that Edinburgh Research Explorer content complies with UK legislation. If you believe that the public display of this file breaches copyright please contact openaccess@ed.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.
The inflammatory milieu is the natural habitat for a pathogenic infection, characterised by activity of pro-inflammatory signalling pathways and inflammatory cytokines. Viral entry rapidly activates a range of innate-immune signalling events such as the activation of Pattern Recognition Receptors (PRRs) [1–5]. A virus must therefore counteract intrinsic cellular and innate-immune responses to successfully complete the replication cycle. Frequently this is accomplished by encoding viral effector molecules that block these cellular responses by working as either structural or functional mimics of host target proteins [6–11]. Nuclear DNA viruses are dependent on the host transcriptional machinery to express the first viral genes; for example the immediate-early (IE) control elements of DNA viruses are by definition absolutely dependent on host transcription factors (TF) [12]. Therefore, these viruses are particularly hostage to their host transcriptional environment [13,14]. Here we propose that mimicry of regulatory DNA sequences by viral regulatory regions may also provide an additional strategy to counteract at IE times of infection the innate-immune response. In this context, viral IE control elements might functionally mimic innate-immune enhancers, taking advantage of the activated immune signalling TFs for promoting viral IE gene expression.

In other words: “If you can’t beat ’em, Join ‘em.”

In exploring this possibility, we present a synopsis of the promoter-regulatory elements from seven extensively studied mammalian viruses with a DNA stage, and seven promoters representing prototypical cellular innate-immune genes. These are the SV-40 early enhancer, the E1A enhancer of HAdV5, the long terminal repeat (LTR) of HIV-1, the E6/7 long control region (LCR) of both HPV-16 and HPV-18, the major IE (MIE) enhancer of HCMV, and the enhancer-1 (Eh-1) regulatory region of HBV for viral sequences, and the enhancer regions of human IFNβ1, IFNG, TNF, IRF1, IL6, IL12B, and IL1B for host sequences. First, we consider similarities between the primary sequence structures of the enhancers. Second, we present arguments for convergent evolution and structural flexibility inherent to enhancer sequences. Third, we discuss functional features and regulatory hallmarks that may be used to define viral enhancer mimicry of cellular immune enhancers.

**Do Viral and Cellular Enhancers Display Any Primary Sequence Similarity?**

To investigate if there is any similarity of primary sequences and therefore structural mimicry between the selected viral and cellular enhancers, we used the BLAST tool to compare the sequences against each other (Table 1) and applied an exhaustive pairwise multi-way alignment (CloneManager suite 7.0) to search for similarities in this group of sequences (Figure 1A). While multi-way alignment of the various selected viral and cellular promoter-regulatory regions (Figure 1A, top panel) reveals a lack of extended primary sequence homology, the pairwise BLAST comparison showed that small islands of sequence identity or high similarity are present (Table 1). We randomly compared some of these short sequence motifs with the JASPAR CORE (Vertebrates) database [15] and found that all checked motifs have similarities with consensus binding motifs for TFs (e.g., AP1, SP1, YY1, or RelA with relative scores of >0.8). This finding raises the question of whether there might be functional similarity. We therefore consider in the next section how convergent evolution of viral enhancers may have resulted in functional mimicry of the transcription control elements of innate-immune genes, providing a co-opting strategy for immune evasion.

**Could Viral Regulatory Regions Evolve as Functional Mimics of Innate-Immune Enhancers without Extensive Sequence Similarity?**

There are two principal genetic mechanisms that could lead to viral mimicry of host enhancers, horizontal transfer of cellular sequences to viral genomes or genetic drift of viral sequences. The first possibility, acquisition of cellular sequences through horizontal sequence transfer, could arise through illegitimate recombination with host DNA, for example by retro-transposition of non-coding RNA transcripts, resulting in the virus hijacking host transcription control sequences. If this were the general case, we would, however, expect significant structural similarity,
which we did not find in our analysis. Alternatively, but not mutually exclusive from horizontal transfer, viral enhancer mimics could arise through neutral evolution and genetic drift by sequence duplication or accumulation of point mutations. Duplicated sequence features are hallmarks for many viral and cellular enhancers [16–24]. For instance, deletion or loss of enhancer sequences in SV40 and JC polyomavirus promotes restoration of enhancer function through duplication of flanking sequences [25–28]. A third possibility is the accumulation of point mutations in enhancer sequences and subsequent fixation [29]. It has recently been described for a wide range of species that evolution of host-cell transcriptional control can occur in relatively short time spans and is mainly driven by the rapid and flexible emergence or loss of binding motifs rather than by evolution of the TF proteins themselves [30–36]. The described mechanisms of rapid enhancer evolution argue that viral enhancers could acquire functionality that mimics innate-immune enhancers without any extensive sequence homology, and this is consistent with the comparison of cellular and viral enhancers shown in Figure 1A. This possibility is underscored by the fact that promoter sequences seem to be poorly conserved even among members within a virus-family yet share many of the same regulatory elements [37]. For example the MIE enhancers of cytomegaloviruses show low levels of primary sequence similarity between the different species strains (Figure 1A, lower panel). Despite these differences, functionality of the enhancers is conserved between hosts for different CMV species strains, e.g., the human CMV enhancer can functionally complement deletion of the murine CMV enhancer [38] and human CMV enhancer sequences recapitulate in vivo biological sites of infection in species from mice to zebra fish [39–41].

Table 1. Summary of pairwise sequence comparison.

| Host   | Selected enhancer region | Number of small islands of high similarity (BLAST) | IFNG | IFNB1 | IL18 | IL12B | TNF | IRF1 | IL8 |
|--------|--------------------------|---------------------------------------------------|------|-------|------|-------|-----|------|-----|
| Viral  | HCMV (2), IFNB1 (1), IL8 (1), IL18 (1), IFNB1 (1), IL8 (2), IIIA (1), HAdV5 (2), HPV-16 (1), HPV-18 (1), HPV-16 (1), HBV (1) | IFNG (1), IL8 (2), IIIA (2), HPV-16 (1), HPV-18 (1), HPV-16 (1), HBV (1), HPV-16 (1), HBV (1), HPV-16 (1) | IFNG (1), IL8 (1), IIIA (1), HAdV5 (1), HPV-16 (1), HPV-18 (1), HPV-16 (1), HBV (1), HPV-16 (1), HBV (1), HPV-16 (1) | IFNG (1), IL8 (1), IIIA (1), HAdV5 (1), HPV-16 (1), HPV-18 (1), HPV-16 (1), HBV (1), HPV-16 (1), HBV (1), HPV-16 (1) | IFNG (1), IL8 (1), IIIA (1), HAdV5 (1), HPV-16 (1), HPV-16 (1), HBV (1), HPV-16 (1), HBV (1), HPV-16 (1), HBV (1), HPV-16 (1) | IFNG (1), IL8 (1), IIIA (1), HAdV5 (1), HPV-16 (1), HPV-16 (1), HBV (1), HPV-16 (1), HBV (1), HPV-16 (1), HBV (1), HPV-16 (1) | IFNG (1), IL8 (1), IIIA (1), HAdV5 (1), HPV-16 (1), HPV-16 (1), HBV (1), HPV-16 (1), HBV (1), HPV-16 (1), HBV (1), HPV-16 (1) | IFNG (1), IL8 (1), IIIA (1), HAdV5 (1), HPV-16 (1), HPV-16 (1), HBV (1), HPV-16 (1), HBV (1), HPV-16 (1), HBV (1), HPV-16 (1) | IFNG (1), IL8 (1), IIIA (1), HAdV5 (1), HPV-16 (1), HPV-16 (1), HBV (1), HPV-16 (1), HBV (1), HPV-16 (1), HBV (1), HPV-16 (1) |
### A

| Gene   | AT-rich | GC-rich |
|--------|---------|---------|
| IL1B   |         |         |
| HAadV5 |         |         |
| IFNB   |         |         |
| IFNG   |         |         |
| IL12B  |         |         |
| IFN1   |         |         |
| HIV-1  |         |         |
| TNF    |         |         |
| HBV    |         |         |
| HCMV   |         |         |
| IL8    |         |         |
| SV40   |         |         |
| HPV16  |         |         |
| HPV18  |         |         |

### B

Host

22 TFs

21 TFs

29 TFs

Virus

### C

- **IFNG [10/16]**
- **IFNB [6/13]**
- **TNF [8/9]**
- **IRF1 [5/8]**
- **IL1B [7/10]**
- **IL8 [6/10]**
- **IL12B [3/8]**

**Network Diagram**

- **ETS**
- **HMG1**
- **NFIAT**
- **CREB/ATF**
- **YY1**
- **SP1**
- **Ap1**
- **NFkB**
- **C/EBP**
- **RAR**
- **STATs**
- **Oct**
- **SRF**

**Nodes and Edges**

- [6/4] SV40
- [9/17] HIV-1
- [6/8] HPV-16/18
- [11/17] HCMV
- [5/16] HBV
- [3/5] HAadV5
**Figure 1. Comparison of host innate-immune and viral regulatory regions.** A) Multi-way alignment of analysed enhancer sequences shows no sequence similarity. Narrow grey boxes mark AT-rich stretches and dark grey boxes mark GC-rich stretches. Overall, sequence similarity was too low to produce a phylogenetic tree. To analyse sequence similarity within one family of viruses, we compared the major immediate-early enhancer region of rat-CMV (RCMV) with those of human (HCMV), murine (MCMV), chimpanzee (CCMV) and rhesus (RHCMV) cytomegalovirus. Small stretches of sequences similarity to the RCMV sequence are indicated by wide light grey boxes (similarity >80%). B) Venn diagram of 72 TFs identified in our literature search to interact with the analysed regulatory sequences. Detailed SBGN diagrams of all elements and interactions can be found at [46–52] except for TNF [57]. C) Simplified summary of transcription factor families shared between analysed innate-immune regulatory regions and viral control elements. For simplification interactions with members belonging to a family of TFs are represented by only one symbol (e.g., p50, p65, and RelA interactions are all represented by the “NFkB” symbol). The summary was produced in the “MSc by research in genomics and pathway biology” project by literature review. Digits in brackets indicate the number of shared interactions (left of dash) and total number of interactions for the specific enhancer (right of dash). TFs that are more highly connected with viral and host elements were placed toward the centre.

doi:10.1371/journal.ppat.1003804.g001

**Table 2. List of identified interactions for the selected viral and host enhancers.**

| TF Name | Entrez Gene ID | Protein Family | TF Name | Entrez Gene ID | Protein Family |
|---------|----------------|----------------|---------|----------------|----------------|
| NFKB1 (p50) | 4790 | NFkB | MYOF | 26509 | Ferlin |
| RelA (p65) | 5970 | NFkB | HSF1 | 3297 | HSF |
| RelC | 5966 | NFkB | ELK1 | 2002 | ETS |
| NFKB2 (p52) | 4791 | NFkB | SRF | 6722 | SRF |
| C/EBP | N/A (generic) | C/EBP | RAR | 5914 | Nuclear hormone receptor |
| CREB1 | 1385 | bZIP | RXR | 6256 | Nuclear hormone receptor |
| ATF1 | 466 | AP | ETS2 | 2114 | ETS |
| ATF2 | 1386 | AP | GAP12 | Unspecified | Unspecified |
| AP1/Jun | 3725 | AP | NRF (NKRF) | 55922 | N/A |
| FOS | 2353 | AP | NF1 | 4763 | Nuclear hormone receptor |
| SP1 | 6667 | C2H2-zinc finger | GRE/NR3C1 | N/A (generic) | Nuclear hormone receptor |
| SP1I | 6688 | ETS | AP2 | 7020 | AP |
| HMGI(Y) | 3159 | HMG | AP3 | Unspecified | Unspecified |
| OCT 1 | 5451 | OCT/POU | USF1 | 7391 | Helix-loop-helix leucine zipper |
| OCT 2 | 5452 | OCT/POU | TFE3 | 7030 | MIF/TFE |
| IRF1 | 3659 | IRF | LEF1 | 51176 | TCF/LEF |
| IRF2 | 3660 | IRF | ETS1 | 2113 | ETS |
| IRF3 | 3661 | IRF | OTK18 | 7728 | Krueppel C2H2-zinc finger |
| IRF7 | 3665 | IRF | E2F1 | 1869 | EF |
| STAT1 | 6772 | STAT | BCL3 | 602 | N/A |
| STAT2 | 6773 | STAT | SP3 | 6670 | C2H2-zinc finger |
| STAT3 | 6774 | STAT | ERF | 2077 | ETS |
| STAT4 | 6775 | STAT | GF11 | 2672 | C2H2-zinc finger |
| NFATp/NFATc | 4773/511224 | NFAT | CUX1 | 1523 | N/A |
| NFIL6 | 1051 | bZIP | E1A | 6870514 | Adenoviridae E1A protein |
| YY1 | 7528 | YY | E4F1 | 1877 | EF |
| TBX21 | 30009 | T-BOX | TAF1 | 6872 | TAF1 |
| EOMES | 8320 | T-BOX | HBS1L | 10767 | N/A |
| PPAR | N/A (generic) | Nuclear hormone receptor | HNF1 | 6927 | Hepatic nuclear factor |
| PPAR/GROX1 | 5468/5629 | Nuclear hormone receptor | HNF3 | 2305 | Hepatic nuclear factor |
| SMAD3 | 4088 | SMAD | HNF4 | 3172 | Hepatic nuclear factor |
| RUNX3 | 864 | N/A | RXF1 | 5989 | RXF |
| PRDM1/PRDI BF1 | 639 | C2H2-zinc finger | PX | 944566 | Orthohepadnavirus protein X |
| HIVE2/PRDI BF1 | 3097 | C2H2-zinc finger | C- abl | 25 | Tyr protein kinase family |
| HIVE1 | 3096 | C2H2-zinc finger | NR2F1/COUP-TF | 7025 | Nuclear hormone receptor |
| NREBP | 6651 | N/A | PEF1 | 553115 | Penta-EF-hand protein |

doi:10.1371/journal.ppat.1003804.t002
inflammatory signalling. In the following section we briefly discuss these hallmarks.

**Shared Transcription Factor Interactions**

The human genome encodes an estimated 1,700 to 1,900 TFs, with 1,391 representing high-confidence candidates [42]. These proteins represent an ample resource for viruses to harness. To probe, in more detail, the TF usage of the 14 viral and innate-immune enhancers selected (Table 1), we constructed unambiguous diagrams [43–45] of known TF interactions—available as an online resource on Figshare [46–52]. Using this approach we identified 72 interactions (Table 2) between the selected host and viral regulatory regions and host TFs. Of the 72 interactions identified, 43 were described for cellular enhancers and 50 for viral enhancers and 21 interactions (49% and 42% respectively) are shared among innate-immune enhancers and viral enhancers (Figure 1B). Annotation of this dataset using the BioMART tool (v0.7, ENSEMBL release v72) identified 31 TFs associated with “regulation of immune processes” (GO:0002376) in our 72 identified interactions. Notably, the extent to which the distinct viral enhancers share factors with the innate-immune genes varies (Figure 1C). This may be explained by the different physiological roles of the innate-immune genes and lifestyles of the selected viruses. Among the viruses, HCMV and HIV-1 enhancers show the largest TF overlap in total numbers of interactions with the innate-immune genes. In summary, we identified a substantial overlap in TF interactions between host and viral regulatory regions.

**Comparable Expression Kinetics**

It is noteworthy that host immediate-early response genes and viral immediate-early genes are, by definition, identified by the same criterion, namely that their expression is independent of newly synthesised proteins [12,53,54]. Upon infection of permissive cells, viral promoters are activated within the first hour of infection. This follows a typical expression profile with a peak between 2–6 h followed by reduced expression levels. This expression pattern has parallels with the temporal expression of host innate-immune genes, e.g., IFNB1, IL6, or TNF that are rapidly induced after PRR activation [55–58]. Most notably, it has recently been demonstrated in a genome-wide transcriptome study with murine CMV that the mRNA synthesis rate of viral IE transcripts is rapidly induced and subsequently strongly downregulated, following the expression kinetic profile for many innate immune genes in this dataset [59].

**Response to Immune-Stimulatory Ligands**

A corollary of viral enhancer mimicry of innate-immune regulatory functions is that the viral promoters/enhancers should be activated by the same signalling events as innate-immune genes. This implies that events during the infection process that trigger “antiviral” signalling cascades actually facilitate the initial viral transcription. In this context, it has been shown that activation of TLRs by LPS and CpG [60,61] increases activity in isolated HCMV-enhancer and HIV-LTR–driven reporter constructs [62–64]. This also seems to apply in the context of viral infection since cytokine signalling stimulates HBV gene expression [65] and HIV needs TLR-8 signalling in specific cell types for replication [66]. It is also notable that all of the viral control regions examined here have been shown to interact with AP-1 (Figure 1C). While AP-1 is not exclusively associated with innate-immune signalling, it can be activated by TLR signalling via MAPK-activation or by cAMP-related signalling during infection [67,68] and subsequently also binds to innate-immune enhancers. Taken together, these examples indicate that so-called “antiviral” processes have the potential to facilitate viral IE gene expression and replication. In the future, their importance and potentially proviral role should be examined in viral infection models.

**Responsiveness to Negative Feedback Control**

Immune signalling pathways are tightly regulated by negative feedback with the inhibitors of signalling activity acting in a matter of minutes to hours [69,70]. Thus, innate-immune negative feedback loops should also inhibit viral gene expression and may play a role in viral latency. This hallmark of viral enhancer mimicry might prove the most challenging for scientific investigation. Interference with negative feedback regulators before infection may lead to an exacerbated immune response, either inducing an elevated antiviral state in the cell before the experimental infection or driving it into apoptosis. Still, proving that this hallmark is applicable to viral infections might provide new drug targets to inhibit viral infections. While, to our knowledge, no direct effects of negative regulators of inflammatory signalling on viral gene expression have been reported so far, it has been shown that anti-inflammatory drugs and chemical inhibitors of pro-inflammatory signalling, expected to increase viral replication, actually can inhibit viral gene expression and replication of HCMV, HBV, and HIV-1 [67,68,71–74].

**Concluding Remarks**

TFs activating innate-immune genes are regulated by PRR signalling that cannot be efficiently inhibited by viruses as their activation occurs during the viral entry process. Mimicking an innate-immune enhancer therefore has the advantage that TFs, already activated by the viral entry process, can be directly utilised in a time restricted manner to ensure viral gene expression at IE times. We hope this opinion opens debate and provides new insights for either reexamination or future-based investigations toward understanding viral gene activation and latency. Indeed we believe that the principle of viruses co-opting host-innate regulatory signals has broad implications toward understanding the biological role of viral enhancers, in acute and latent viral infections, and prospective host-directed antiviral therapeutic and vaccine strategies.

**Acknowledgments**

Our special thanks to Steven Watterson for organising the Figshare online resource, Kevin Robertson for editorial suggestions, Richard Perry for help with compiling the figures, and Venkatesh Mallikarjun, Chen Sz-Hau, Ming-Yuan Huang, David MacDonald, Aditi Yadaf, Zuchra Zakirova, Julia Weber, and Mohammed Ba Abdullah for their student project reports (coordinated by Douglas Roy) on viral and cellular promoters as partial fulfilment of MSc by research in “Genomics and Pathway Biology.”

**References**

1. Tabeta K, Georgel P, Janssen E, Du X, Hohe K, et al. (2004) Toll-like receptors 9 and 3 as essential components of innate immune defense against mouse cytomegalovirus infection. Proc Natl Acad Sci U S A 101: 3516–3521.

2. Kumar H, Kawai T, Akira S (2011) Pathogen recognition by the innate immune system. Int Rev Immunol 30: 16–34.

3. Kawai T, Akira S (2006) TLR signaling. Cell Death Differ 13: 816–825.

4. Zhong B, Tien P, Shu HB (2006) Innate immune responses: crosstalk of signaling and regulation of gene transcription. Virology 352: 14–21.

5. O’Neill LAJ, Goedbloed D, Bowir AG (2013) The history of Toll-like receptors - redefining innate immunity. Nat Rev Immunol 13: 453–460.

6. Elde NC, Malik HS (2009) The evolutionary conundrum of pathogen mimicry. Nat Rev Micro 7: 787–797.

7. Wu B, Hur S (2013) Viral counterattack against the host innate immune system. Cell Res 23: 735–736.

8. Drayman N, Glick Y, Ben-nun-Shaul O, Zer H, Zlotnick A, et al. (2013) Pathogens use structural
mimicry of native host ligands as a mechanism for host receptor engagement. Cell Host Microbe 14: 63–73.

9. Sloebdeman B, Barry PA, Spencer JV, Avdic S, Ahammad M (2009) Virus-encoded homology of cellular interleukin-10 and their control of host immune function. J Virol 83: 9618–9629.

10. Alcamí A (2003) Viral mimicry of cytokines, chemokines and their receptors. Nat Rev Immunol 3: 36–50.

11. Engel P, Angulo A (2012) Viral immunomodulatory proteins usurping host genes as a survival strategy. In: López-Larrua C, editors. Self and non-self. Springer US, pp.256-276.

12. Honess RW, Roizman B (1974) Regulation of herpesvirus macromolecular synthesis I. Cascade reversion to the synthesis of three groups of viral proteins. J Virol 14: 18–25.

13. Ghazal P, Garcia-Ramirez J, Kurz S, Angulo A (2000) Viruses: hostages to the cell. Virology 275: 233–257.

14. Ghazal P, Garcia-Ramirez J, Gonzalez AJC, Angulo A (2000) Principles of homeostasis in governing virus activation and latency. Virology 268: 19–23.

15. Bryne JC, Valen E, Tang MHE, Marriott T, Winther O, et al. (2008) JASPAR, the open access database of transcription factor-binding profiles: new content and tools in the 2008 update. Nucl Acids Res 36: D102-D106.

16. Boshart M, Weber F, Jahn G, Dorsch-Hasler K, Fleckenstein B, et al. (1985) A very strong SV40 enhancer trap incorporates exogenous regulatory sequences and their role in the regulation of class I gene expression. Cell 44: 639–650.

17. Harlan SM, Reiter RS, Sigmund CD, Lin JL-C, Tucker C, et al. (1996) Developmental analysis of the human cytomegalovirus immediate-early gene promoter (UL123) in zebrafish. Gene 205: 101–105.

18. Koedood M, Fichtel A, Meier P, Mitchell PJ, Winther O, et al. (2008) JASPAR, the open access database of transcription factor-binding profiles: new content and tools in the 2008 update. Nucl Acids Res 36: D102-D106.

19. Lee W, Hashlinger A, Karin M, Tjian R (1987) Activation of transcription by two factors that can act like an enhancer element. Proc Natl Acad Sci U S A 84: 1018–1022.

20. Beutler B, Jiang Z, George P, Crow M, Criner B, et al. (2006) Genetic analysis of host resistence: Toll-like receptor signalling and immunity at large. Annu Rev Immunol 24: 353–389.

21. Lau LF, Nathans D (1987) Expression of a set of growth-related immediate early genes in BALB/c 3T3 cell: coordinate regulation with c-fos or c-myC. Proc Natl Acad Sci U S A 84: 1102–1106.

22. Takaoka A, Yanai H (2006) Interferon signalling network in innate defence. Cell Microbiol 8: 907–919.

23. Grasso RJ, Buchanan JM (1969) Synthesis of early RNA in bacteriophage T4-infected Escherichia coli. Nature 223: 66–74.

24. Angulo A, Messere M, Koszinowski UH, Ghazal P (1998) Enhancer requirement for murine cytomegalovirus growth and genetic complementation by the human cytomegalovirus. J Virol 72: 8502–8509.

25. Koedood M, Fichtel A, Meier P, Mitchell PJ, Winther O, et al. (2008) JASPAR, the open access database of transcription factor-binding profiles: new content and tools in the 2008 update. Nucl Acids Res 36: D102-D106.

26. Nakamichi K, Kishida S, Tanaka K, Suganuma M (1997) Activation by diverse xenochemicals of type-1 interferon response in human cells. FEBS Lett 415: 279–282.

27. Nakamichi K, Kishida S, Tanaka K, Suganuma M (1997) Activation by diverse xenochemicals of type-1 interferon response in human cells. FEBS Lett 415: 279–282.

28. Nakamichi K, Kishida S, Tanaka K, Suganuma M (1997) Activation by diverse xenochemicals of type-1 interferon response in human cells. FEBS Lett 415: 279–282.

29. Nakamichi K, Kishida S, Tanaka K, Suganuma M (1997) Activation by diverse xenochemicals of type-1 interferon response in human cells. FEBS Lett 415: 279–282.
important for viral replication. J Virol 79: 5035–5046.

63. Equils O, Faure E, Thomas L, Buhat Y, Trushin S, et al. (2001) Bacterial lipopolysaccharide activates HIV long terminal repeat through Toll-like receptor 4. J Immunol 166: 2342–2347.

64. Zimmernann A, Trilling M, Wagner M, Wilborn M, Babic I, et al. (2003) A cytomegaloviral protein reveals a dual role for STAT2 in IFN-γ signaling and antiviral responses. J Exp Med 201: 1543–1553.

65. Waris G, Siddiqui A (2002) Interaction between STAT3 and HNF-4 leads to the activation of liver-specific hepatitis B virus enhancer 1 function. J Virol 76: 2721–2729.

66. Gringhuis SI, van der Vlist M, van den Berg LM, den Dunnen J, Litjens M, et al. (2010) HIV-1 exploits innate signaling by TLR8 and DC-SIGN for productive infection of dendritic cells. Nat Immunol 11: 419–426.

67. Mocarski ES (2002) Virus self-improvement through inflammation: no pain, no gain. Proc Natl Acad Sci U S A 99: 3362–3364.

68. Zhu H, Gong JP, Yu D, Breenahan WA, Shenk TE (2002) Inhibition of cyclooxygenase-2 blocks human cytomegalovirus replication. Proc Natl Acad Sci U S A 99: 3932–3937.

69. Schroder K, Hertzog PJ, Ravasi T, Hume DA (2004) Interferon-gamma: an overview of signals, mechanisms and functions. J Leukoc Biol 75: 163–189.

70. Lacaze P, Raza S, Sing G, Page D, Forster T, et al. (2009) Combined genome-wide expression profiling and targeted RNA interference in primary mouse macrophages reveals perturbation of transcriptional networks associated with interferon signalling. BMC Genomics 10: 372.

71. Speir E, Yu ZX, Ferrans VJ, Huang ES, Epstein SE (1998) Aspirin attenuates cytomegalovirus infectivity and gene expression mediated by cyclooxygenase-2 in coronary artery smooth muscle cells. Circ Res 83: 210–216.

72. Fiorino S, Cursaro C, Lorenzini S, Loggi E, Brodosi L, et al. (2011) The pharmacology and activity of non-steroidal anti-inflammatory drugs (NSAIDs); a review of their use as an adjunctive treatment in patients with HBV and HCV chronic hepatitis. Ital J Med 5: 82–89.

73. Kopp E, Ghosh S (1994) Inhibition of NF-kappa B by sodium salicylate and aspirin. Science 265: 956–959.

74. DeMeritt IB, Podduturi JP, Tilley AM, Nogalski MT, Yurochko AD (2006) Prolonged activation of NF-kappaB by human cytomegalovirus promotes efficient viral replication and late gene expression. Virology 346: 15–31.