GitHub Figure 1. Analyses of the virus-inducible H3K27ac-ChIP-seq signals in human monocytes (THP-1). (A) QRTMs on H3K27ac-ChIP-seq virus-inducible signals in THP-1 human monocytes (centered ±2 kb); Aggregation plots (signals' average) and heatmaps (signals' coverage) illustrate the gradual enrichment of IRF3 signals as shaped during the transition from naïve to antiviral cell states in THP-1 (SVI; 0h, 6h). **(B)** Upper panel: Genomic localization assessments highlight the distribution of the H3K27ac across the human genome in virus-infected cells (SVI 6h). Lower panel: Analysis of the lexicon of TFBSs elucidates DNA grammar characteristics legible, among others, by members of the microbial-activated families of TFs, e.g., IRFs, STATs, JUN, etc. Right panel: GOs show substantial specificity for defense and immune-response cellular processes in virus-infected cells (SVI 6h).

GitHub Figure 2. Striking examples of human SHAe with DNA sequences conserved in viral genomes. Same as in Figure 8A. Striking examples of SHAe that are classified in e-primates, e-mammals, and b-mammals and encompass DNA sequences that exhibit high conservation with viral genomes.

GitHub Figure 3. Integrative analyses of SHAe loci that are enriched in SNPs linked to Human Autoimmune diseases. (A) Upper left panel: A description of the workflow. Upper center panel**:** The transcriptional and epigenomics states of the p65-SHAe and its flanking ±2.5 kb sequence. These genomic coordinates are encompassed within the *IRF7* genomic locus. Several autoimmune-disease-associated SNPs are mapped within the above genomic coordinates, and the majority of those are linked to Systemic lupus erythematosus (SLE). Upper right panel: A catalog of the SNPs and their associated Human autoimmune diseases. **(B)** Upper panel: The evolutionary origins of the SHAe, its flanking ±2.5 kb sequence, and its *in cis* associated SNPs within the cohort of 100 representative vertebrate species (phylop100way); In principle, the chr11:612,739-618,229 locus of the human genome is traced primarily in species of mammals and primates, and lower sequence conservation is observed in other vertebrates, such as Alligator. Middle panel: The sequence architecture of the chr11:612,739-618,229 locus of the human genome. TFBSs for IRF1/3 (green letters) and NFκB (red letters), the p65-SHAe (blue shadow), and the SNPs (brown letters) are highlighted. Lower panel: Linkage disequilibrium (LD) analyses performed by the calculation of the squared correlation (r^2) between SNPs within European ancestry populations. A pair-wised approach was conducted for the total of SNPs and the results highlighted significant correlations with the rs1061502-rs1131665, rs112006329-rs1131665, and rs112006329-rs1061502 pairs classified at the top of the ranking, reaching an absolute correlation. All these SNPs are associated with SLE. Part of the Figure was created in BioRender: Agelopoulos, M. (2025) https://BioRender.com/l95g665

GitHub Figure 4. Integrative analyses of SHAe loci that are enriched in SNPs linked to Human Autoimmune diseases. (A) Upper left panel: A description of the workflow. Upper center panel: The transcriptional and epigenomics states of the IRF3/p65-SHAe and its flanking ±2.5 kb sequence. A CH is assembled prior to and becomes enhanced upon virus-infection (SVI 0h, 3h, 6h) accompanied by the binding of the antimicrobial TFs (IRF3 and p65) and the recruitment of CBP, thus leading to the *in vivo* reconstitution of functional vrCRMs. Two autoimmune-disease-associated SNPs are mapped within the above genomic coordinates. Interestingly rs6451493 inhabits the IRF3/p65-SHAe sequence, as shown in (B) (sequence panel). Upper right panel: A catalog of the SNPs and their associated Human autoimmune diseases. **(B)** Upper panel: The evolutionary origins of the SHAe, its flanking ±2.5 kb sequence, and its *in cis* associated SNPs within the cohort of 100 representative vertebrate species (phylop100way); In principle, the chr5:40,408,427-40,414,103 locus of the human genome is not traced beyond mammalian species, and its sequence conservation is observed from lower mammals such as Armadillo to primates. Middle panel: The sequence architecture of chr5:40,408,427-40,414,103 coordinates of the human genome. TFBSs for IRF1/3 (green letters) and NFκB (red letters), the IRF3/p65-SHAe (blue shadow), and the SNPs (brown letter) are highlighted. Lower panel: Linkage disequilibrium (LD) analyses performed by the calculation of the squared correlation (r^2) between SNPs within European ancestry populations. A pair-wised approach was conducted for the total of SNPs and the results highlighted significant correlations with the rs11742570-rs6451493 pair classified at the top of the ranking, reaching an absolute correlation. Both SNPs are associated with ULC, whereas the rs11742570 is also associated with CD. Part of the Figure was created in BioRender: Agelopoulos, M. (2025) https://BioRender.com/o60a340

GitHub Figure 5. Integrative analyses of SHAe loci that are enriched in SNPs linked to Human Autoimmune diseases. (A) Upper left panel: A description of the workflow. Upper center panel: The transcriptional and epigenomics states of the p65-SHAe and its flanking ±2.5 kb sequence. These genomic coordinates encompass an extended part of the *JAK2* genomic locus and its TSS upstream sequences. A CH is assembled prior to and upon virus-infection (SVI 0h, 3h, 6h) accompanied by the binding of the antimicrobial TFs (IRF3 and p65), thus leading to the *in vivo* reconstitution of functional vrCRMs. A unique autoimmune-disease-associated SNP is mapped within the above genomic coordinates, and it is linked to Systemic Lupus Erythematosus (SLE) (Upper right panel). **(B)** Upper panel: The evolutionary origins of the SHAe, its flanking ±2.5 kb sequence, and its *in cis* associated SNP within the cohort of 100 representative vertebrate species (phylop100way); In principle, the chr9:4,984,079-4,989,381 locus of the human genome is not traced beyond mammalian species, and its sequence conservation is significantly increased from lower mammals, such as Armadillo, to primates. Middle panel: The sequence architecture of chr9:4,984,079-4,989,381 coordinates of the human genome. TFBSs for IRF1/3 (green letters) and NFκB (red letters), the p65-SHAe (blue shadow), and the SNP (brown letter) are highlighted. Part of the Figure was created in BioRender: Agelopoulos, M. (2025) https://BioRender.com/t86g404

GitHub Figure 6. Integrative analyses of SHAe loci that are enriched in QTL associated with Human Immune-related diseases. (A) Upper left panel: A description of the workflow. Upper center panel: The transcriptional and epigenomics states of the IRF3/p65-SHAe and its flanking ±2.5 kb sequence. A unique immune-disease-associated QTL is mapped within the above genomic coordinates, and it is linked to Crohn's disease (CD) and Inflammatory Bowel Disease (IBD) (Upper right panel). **(B)** Upper panel: The evolutionary origins of the SHAe, its flanking ±2.5 kb sequence, and its *in cis* associated QTL within the cohort of 100 representative vertebrate species (phylop100way); In principle, the chr10:30,066,920-30,072,468 locus of the human genome is not traced beyond mammalian species, and its sequence conservation is significantly increased from mammals to primates. Middle panel: The sequence architecture of chr10:30,066,920-30,072,468 coordinates of the human genome. TFBSs for IRF1/3 (green letters) and NFκB (red letters), the IRF3/p65-SHAe (blue shadow), and the QTL (brown letter) are highlighted. Part of the Figure was created in BioRender: Agelopoulos, M. (2025) https://BioRender.com/t35u428