

Description of Additional Supplementary Files:

File: Supplementary Data 1

Description: Viral protein signature of Clade Ib and II MPXV MOI 1 infected ISG15 KO vs WT MEF lysates at 21 hours post-infection. Table lists the protein ID, gene name and the log2-fold change (FC) (MPXV infected ISG15 KO MEFs vs infected WT MEFs) of the levels of each protein. Ordered through OPG.

File: Supplementary Data 2

Description: Protein signature of 2022 MPXV MOI 1 infected KO vs WT MEF lysates at 21 hours post-infection. Table lists the protein ID, gene, the log2-fold change (FC) (MPXV infected WT MEFs vs infected ISG15 KO MEFs) of the levels of each protein, and the statistical significance ($-\log P$ value). Ordered from largest to smallest FC.

File: Supplementary Data 3

Description: Protein signature of USA 2003 MOI 1 infected KO vs WT MEF lysates at 21 hours post-infection. Table lists the protein ID, gene, the log2-fold change (FC) (MPXV infected WT MEFs vs infected ISG15 KO MEFs) of the levels of each protein, and the statistical significance ($-\log P$ value). Ordered from largest to smallest FC.

File: Supplementary Data 4

Description: Protein signature of WRAIR MOI 1 infected KO vs WT MEF lysates at 21 hours post-infection. Table lists the protein ID, gene, the log2-fold change (FC) (MPXV infected WT MEFs vs infected ISG15 KO MEFs) of the levels of each protein, and the statistical significance ($-\log P$ value). Ordered from largest to smallest FC. Genes mentioned in manuscript highlighted in bold.

File: Supplementary Data 5

Description: Protein signature of 2024 MPXV MOI 1 infected KO vs WT MEF lysates at 21 hours post-infection. Table lists the protein ID, gene, the log2-fold change (FC) (MPXV infected WT MEFs

vs infected ISG15 KO MEFs) of the levels of each protein, and the statistical significance ($-\log P$ value). Ordered from largest to smallest FC. In bold, mentioned proteins in manuscript.

File: Supplementary Data 6

Description: Candidate viral proteins ISGylated during 2024 and 2022 MPXV infection in HeLa cells. Table lists the MPXV virus, Protein ID, OPG, MPXV Protein, VACV Protein Homologue and Function.

File: Supplementary Data 7

Description: Source data including experiment values and TIFF images.