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Supplemental information

Riok3 inhibits the antiviral

immune response by facilitating

TRIM40-mediated RIG-I and MDA5 degradation

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Table S1: E3 ligases interacting with both RIG-I and MDA5 from PPI database, Related to Figure 5.

A systematic database and literature search was performed to identify the E3 ligases interacting with both RIG-I and MDA5. 32 candidates were found to be interacting with both proteins. After filtering the candidates without literature support and those that only performing K-63 ubiquitin. Three E3 ligases (TRIM40, Parkin and RNF125) were screened out.

| E3 ligases | Function in virology | Ubiquitination mode of RLRs | References |
|------------|--|-----------------------------|---|
| RNF125 | Promote SeV via degrading RIG-I and MDA5 Inhibit SeV and NDV via repressing TRIM14 | K-48 | PMID: 17460044 PMID: 28476934 |
| RNF135 | Inhibit many viruses (e.g. VSV/SeV/IAV/IBV/ HCV) via activating RIG-I | K-63 | PMID: 19017631 PMID: 21147464 PMID: 23950712 PMID: 31006531 PMID: 31335993 |
| RAD18 | Promote EBV infectivity via interacting with BPLF1 Inhibit HIV-1/MLV/VSV via binding DNA intermediates | No report | PMID: 16710452 PMID: 24672041 PMID: 30935695 |
| NSMCE1 | | No report | |
| SHPRH | | No report | |
| Parkin | Promote SeV/VSV via degrading RIG-I and MDA5 | K-48 | PMID: 32983119 |
| TRIM4 | Inhibit VSV/SeV via activating RIG-I | K-63 | PMID: 24755855 |
| TRIM5 | Inhibit retroviruses via multiple mechanisms | No report | PMID: 31312031 |
| TRIM6 | Promote EboV via enhancing ubiquitination of VP35 | No report | PMID: 28679761 |
| TRIM8 | Inhibit HIV/IAV via maintaining IRF7 to induce IFN α/β | No report | PMID: 31799391 |
| TRIM13 | Inhibit EMCV/IAV via inhibition of MDA5 activity | No report | PMID: 25008915 |
| TRIM17 | | No report | |
| TRIM19 | Inhibit various viruses (e.g. HFV/IAV/EMCV/AAV/VSV/HIV-1) via multiple mechanisms | No report | PMID: 9444998 PMID: 11432836 PMID: 11907221 PMID: 16912307 PMID: 20702643 PMID: 21994459 PMID: 24586174 PMID: 26566030 |
| TRIM21 | Inhibit various viruses via multiple mechanisms | No report | PMID: 31555278 |
| TRIM22 | Inhibit many viruses (e.g. HIV/HBV/IAV/HCV/RSV) via various mechanisms | No report | PMID: 28782753 PMID: 32803897 |
| TRIM24 | Inhibit VSV via mediating K63-linked TRAF3 ubiquitination Inhibit retroviral transcription via forming a complex with TRIM28 and TRIM33 | No report | PMID: 32324863 PMID: 32932986 |
| TRIM25 | Inhibit various viruses via mediating K63-linked | K-63 | PMID: 17392790 |

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| | ubiquitination of RIG-I | | PMID: 29018447 |
| | Inhibit various viruses via other mechanisms like positively regulating MDA5-MAVS axis, binding viral RNAs and ribonucleoproteins | | PMID: 26299329 PMID: 27528750 |
| TRIM27 | Promote HCV via inhibiting IRF3 and NF- κ B pathways Inhibit HSV-1 via degrading ICP0 | No report | PMID: 25320289 PMID: 30847745 |
| TRIM28 | Inhibit M-MLV via binding to PBS Inhibit M-MLV via interacting with YY1 Promote HIV-1 latency via SUMOylating CDK9 and inhibiting P-TEFb | No report | PMID: 17923087 PMID: 29407374 PMID: 30652970 |
| TRIM31 | Inhibit VSV and SeV via activating MAVS Inhibit HBV via degrading HBx | No report | PMID: 27992402 PMID: 31825835 |
| TRIM32 | Inhibit HSV-1/SeV via promoting K63-linked polyubiquitination of STING Inhibit IAV via degrading PB1 Inhibit HPAIV via interacting with STING | No report | PMID: 22745133 PMID: 26057645 PMID: 28954259 PMID: 32184788 |
| TRIM33 | Inhibit HIV-1 infection via preventing provirus formation Inhibit retroviral transcription via forming a complex with TRIM24 and TRIM28 | No report | PMID: 30804369 PMID: 32932986 |
| TRIM34 | Inhibit HIV via targeting N74D capsids | No report | PMID: 32282853 |
| TRIM38 | Promote VSV via degrading NAP1 Inhibit DNA viruses (e.g. HSV-1/VV/ECTV) via sumoylation of cGAS Inhibit EMCV/NDV/VSV/SeV via sumoylation of RIG-I and MDA5 | No report | PMID: 22539786 PMID: 27637147 PMID: 28250012 |
| TRIM39 | Inhibit iridovirus and nodavirus via repressing viral gene transcription | No report | PMID: 26784918 |
| TRIM40 | Promote VSV/SeV/EMCV via degrading RIG-I and MDA5 | K-48 | PMID: 29117565 |
| TRIM56 | Inhibit various viruses (e.g. IAV/YFV/ZIKV/BVDV/DENV2/SeV/HSV-1) via multiple mechanisms | No report | PMID: 21289118 PMID: 22948160 PMID: 25253338 PMID: 26889027 PMID: 29426904 PMID: 31251739 |
| TRIM59 | Inhibit PRRSV via interacting with nsp11 | No report | PMID: 31683196 |
| TRIM62 | Inhibit VSV/MLV via activating TRIF-TAK1 signaling | No report | PMID: 23077300 |
| TRIM65 | Inhibit EMCV via K63-linked ubiquitination of MDA5 | K-63 | PMID: 28031478 |
| TRIM69 | Inhibit dengue virus via degrading nonstructural protein 3 Inhibit VSV _{IND} via binding phosphoprotein (P) | No report | PMID: 30142214 PMID: 31578292 |
| TRIM71 | | No report | |