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| **Supplementary File 3** | |
| **Protein name/site** | **Biological significance** |
| **TNFA** | |
| K20 | * Jiang et al.(Jiang et al., 2013) described modification of K20 and K19 by long-chain fatty acids. Removal of fatty chains by SIRT6 promotes TNF- secretion |
| **TNFR1B/TNFR2** | |
| K300 | * Novel, no reference found |
| **TNFR1A/TNFR1** | |
| No sites reported in our study. |  |
| **BIRC2/cIAP** | |
| S153 | * N/A, not novel |
| S551 | * N/A, not novel |
| **M3K7/TAK1** | |
| S331 | * Novel, no reference found |
| T333 | * N/A, not novel |
| S367 | * N/A, not novel |
| S375 | * N/A, not novel |
| S389 | * A proteomic study identifies phosphorylation at S389 in response to LPS in macrophages(Wu et al., 2019) * This site is also linked to TAK1 activation(Gallardo et al., 2018) |
| S393 | * N/A, not novel |
| S412 | * Phosphorylation S412 is required for TAK1 activation * S412 phosphorylation occurs in response to LPS in RAW264.7 cells(Kobayashi et al., 2005) * S412 phosphorylation in response to TLR activation contributes to innate immune response(Ouyang et al., 2014) * pS412 is linked to constitutive activation of TAK1 in leukemia and allergy(Watson et al., 2020) |
| S412\_S427 | * N/A, not novel |
| S428 | * N/A, not novel |
| K447 | * N/A, not novel |
| **TAB2** | |
| S353 | * Novel, no reference found |
| S372 | * Mendoza et al.(Mendoza et al., 2008) described phosphorylation at S372 in response to IL-1 in HEK293 and MEFs |
| T376 | * Novel, no reference found |
| S450 | * Fabrik et.al(Fabrik et al., 2018) reported phosphorylation at S450 in response to infection of bone marrow-derived dendritic cells with Francisella tularensis at late infection stage |
| S524 | * Mendoza et al.(Mendoza et al., 2008) described phosphorylation at S524 site in response to IL-1 in HEK293 and MEFs |
| S527 | * N/A, not novel |
| S580 | * N/A, not novel |
| S582 | * Mendoza et al.(Mendoza et al., 2008) described phosphorylation at S582 site in response to IL-1 in HEK293 and MEFs |
| S584 | * Novel, no reference found |
| K653 | * N/A, not novel |
| **TAB3** | |
| S102 | * N/A, not novel |
| S387\_S389 | * N/A, not novel |
| S389 | * N/A, not novel |
| T408 | * Mendoza et al.(Mendoza et al., 2008) described phosphorylation at T408 in response to IL-1 in HEK293 and MEFs * Tao et al.(Tao et al., 2016) reported that phosphorylation at T408 is required for O-GlcNAcylation of S412 |
| S412 | * Tao et al.(Tao et al., 2016) reported S412 O-GlcNAcylation in triple negative breast cancer, which is important for TAK1 activation and influences cell invasion |
| S413 | * N/A, not novel |
| S496 | * N/A, not novel |
| S510 | * Mendoza et al.(Mendoza et al., 2008) describes phosphorylation at S510 in response to IL-1 in HEK293 and MEFs |
| S513 | * N/A, not novel |
| **TRAF1** | |
| S60 | * N/A, not novel |
| S63 | * N/A, not novel |
| S165 | * N/A, not novel |
| K120 | * Novel, no reference found |
| K178 | * This is one of two sites that are ubiquitinated by cIAP2, leading to TRAF1 degradation(Lee et al., 2004) |
| K293 | * Novel, no reference found |
| **TRAF2** | |
| K194 | * Novel, no reference found |
| K313 | * N/A, not novel |
| K331 | * N/A, not novel |
| **NEMO** | |
| S380 | * N/A, not novel |
| K270 | * Huang et al.(Huang et al., 2003) reported sumoylation at K270 and K302 by SUMO-1 in response to DNA damage * Mabb et al.(Mabb et al., 2006) demonstrated K270 and K302 are sumoylated by PIAS in response to genotoxic stress. Interestingly, NEMO sumoylation is also induced by oxidative stress. These events result in NF-kB activation * NEMO sumoylation on k270 is linked to diabetes(Shao et al., 2015) * Liu et al.(Liu et al., 2013) reported that K270 is sumoylated with SUMO-2/3 and desumoylation of this modification by SENP6 is important to dampen activity following TLR3/4 activation |
| K276 | * N/A, not novel |
| K278 | * This residue is ubiquitinated by K63-linked ubiquitin chains in response to NOD2 receptor activation(Abbott et al., 2004). Ubiquitination at K278 is critical for embryonic development(Jun et al., 2013) * Tokunaga et al.(Tokunaga et al., 2009) described ubiquitination of residues K278 and K302 by LUBAC, which is essential for NF-kB activation. Subsequently, Müller-Rischart et al.(Müller-Rischart et al., 2013) reported ubiquitination of these residues by Parkin, which is important response to mitochondrial stress * Hinz et al.(Hinz et al., 2010) reported mono-ubiquitylation at K278 by cIAP1 as a part of genotoxic stress response |
| K302 | * Multiple publications(Huang et al., 2003; Mabb et al., 2006; Shao et al., 2015) reported the significance of K270/K302 sumoylation as described above. Additionally, Niu et al.(Niu et al., 2011) described that K278 and K302 ubiquitination by LUBAC is important step in response to genotoxic stress and that this event is downstream of NEMO nuclear export * See also Müller-Rischart et al.(Müller-Rischart et al., 2013) and Tokunaga et al.(Tokunaga et al., 2009) for NEMO ubiquitination |
| **IKKB** | |
| S670 | * N/A, not novel |
| S672 | * Phosphorylation at S672 was identified in response to LPS(Wu et al., 2019) |
| S675 | * N/A, not novel |
| S679 | * N/A, not novel |
| S689\_S692 | * N/A, not novel |
| S693 | * N/A, not novel |
| S697 | * Phosphorylation at S697 was identified in response to LPS(Wu et al., 2019) |
| K498 | * N/A, not novel |
| K555 | * N/A, not novel |
| **IKKE** | |
| S172 | * Kishore et al.(Kishore et al., 2002) and Shimada et al.(Shimada et al., 1999) described that phosphorylation at S172 is required for the catalytic activity |
| S665 | * N/A, not novel |
| S713 | * N/A, not novel |
| K231 | * Sumoylation at this residue is reported in Renner et al.(Renner et al., 2010). Plays an important role in NF-kB activation following genotoxic stress |
| K241 | * N/A, not novel |
| **IKBZ** | |
| T188 | * Novel, no reference found |
| S189 | * N/A, not novel |
| T192 | * N/A, not novel |
| S262 | * N/A, not novel |
| K5 | * Novel, no reference found |
| K120 | * Novel, no reference found |
| K132 | * Novel, no reference found |
| **NFKB1** | |
| S447 | * N/A, not novel |
| S447\_S452 | * N/A, not novel |
| S896 | * N/A, not novel |
| S897 | * Fujimoto et al.(Fujimoto et al., 1995) reported phosphorylation at S897 as one of two residues by CDK in vitro |
| T942 | * N/A, not novel |
| K275 | * Novel, no reference found |
| K323 | * N/A, not novel |
| **NFKB2** | |
| S222 | * N/A, not novel |
| T425 | * N/A, not novel |
| S680 | * N/A, not novel |
| T682 | * N/A, not novel |
| S858 | * N/A, not novel |
| S871 | * This residue is a part of sites phosphorylated by IKK(Qu et al., 2004; Xiao et al., 2004). |
| **REL** | |
| S321 | * Novel, no reference found |
| S488 | * N/A, not novel |
| **RELB** | |
| S552 | * Marienfeld et al.(Marienfeld et al., 2001) and Neumann et al.(Neumann et al., 2011) report RelB S552 phosphorylation by GSK-3 kinase in T cell following TCR stimulation |
| **RNF31/HOIP** | |
| S377 | * N/A, not novel |
| S441 | * Novel, no reference found |
| S445 | * N/A, not novel |
| S973 | * Novel, no reference found |
| K777 | * N/A, not novel |
| K911 | * Novel, no reference found |
| **OTUL** | |
| K34 | * N/A, not novel |
| K64 | * N/A, not novel |
| K66 | * N/A, not novel |
| K116 | * N/A, not novel |
| **TNAP3/A20** | |
| S217 | * Novel, no reference found |
| S220 | * N/A, not novel |
| S381 | * Phosphorylation at this site by IKK is an important negative regulation mechanism of the NF-kB pathway(Hutti et al., 2007) * p381, and pS480, pS565, pT625, activate A20 DUB activity against K63-linked chains(Wertz et al., 2015) |
| S498 | * N/A, not novel |
| S534 | * N/A, not novel |
| S535 | * N/A, not novel |
| S558\_S563 | * N/A, not novel |
| T567 | * Novel, no reference found |
| S571 | * N/A, not novel |
| S571\_S577 | * N/A, not novel |
| S573 | * N/A, not novel |
| S577 | * N/A, not novel |
| S622 | * Novel, no reference found |
| S730 | * Novel, no reference found |
| K31 | * Novel, no reference found |
| K66 | * N/A, not novel |
| K81 | * N/A, not novel |
| K124 | * N/A, not novel |
| K213 | * Novel, no reference found |
| K526 | * N/A, not novel |
| K594 | * N/A, not novel |
| K620 | * N/A, not novel |
| K628 | * N/A, not novel |
| **TNIP1/ABIN1** | |
| S118 | * N/A, not novel |
| S278 | * N/A, not novel |
| S279 | * N/A, not novel |
| S416 | * N/A, not novel |
| S448 | * N/A, not novel |
| S455 | * N/A, not novel |
| S601 | * Novel, no reference found |
| K288 | * Novel, no reference found |
| K314 | * N/A, not novel |
| K317 | * Novel, no reference found |
| K360 | * N/A, not novel |
| K386 | * Novel, no reference found |
| K402 | * N/A, not novel |
| K465 | * N/A, not novel |
| K480 | * N/A, not novel |
| K522 | * N/A, not novel |
| K525 | * N/A, not novel |
| **TNIP2/ABIN2** | |
| S147 | * N/A, not novel |
| S187 | * N/A, not novel |
| T194 | * Novel, no reference found |
| S196 | * Novel, no reference found |
| S414 | * N/A, not novel |
| K358 | * N/A, not novel |
| **MCL1** | |
| S73 | * Several kinases are implicated in phosphorylating multiple Mcl-1 sites. For example, multiple papers(Choudhary et al., 2015; Chu et al., 2016; Domina et al., 2004; Harley et al., 2010; Nikhil and Shah, 2017) showed that phosphorylation at S73 and T144 is CDK-regulated in mitosis, which is important to induce apoptosis if cells cannot resolve mitotic arrest. In addition, Ding et al.(Ding et al., 2008) shows that Mcl1 is also phosphorylated by Erk. * Inuzuka et al.(Inuzuka et al., 2011) and Wertz et al.(Wertz et al., 2011) demonstrated that phosphorylated Mcl1 is degraded and this requires the Fbw7 F-box protein |
| T144 | * Multiple papers(Choudhary et al., 2015; Chu et al., 2016; Harley et al., 2010; Nikhil and Shah, 2017) report this phosphorylation site. * Inoshita et al.(Inoshita et al., 2002) identifies phosphorylation at T144 by JNK in response to oxidative stress |
| K39 | * Ubiquitination at multiple lysines, including K39 and K178, contributes to Mcl1 stability(Ye et al., 2017). |
| K178 | * Ubiquitination at multiple lysines, including K39 and K178, contributes to Mcl1 stability(Ye et al., 2017). |
| K215 | * N/A, not novel |
| K219 | * N/A, not novel |
| **BID** | |
| S78 | * Phosphorylation of BID at S78 by ATM/ATR is important in preserving genome stability(Kamer et al., 2005; Zinkel et al., 2005) |
| K129 | * N/A, not novel |
| K135 | * N/A, not novel |
| K158 | * N/A, not novel |
| **CASP8** | |
| S60 | * Novel, no reference found |
| S188 | * N/A, not novel |
| S198 | * N/A, not novel |
| S213 | * N/A, not novel |
| K33 | * Novel, no reference found |
| K130 | * N/A, not novel |
| K169 | * N/A, not novel |
| K226 | * N/A, not novel |
| K274 | * Novel, no reference found |
| **CFLAR/cFLIP** | |
| K175 | * Novel, no reference found |
| K390 | * Novel, no reference found |
| **RIPK1** | |
| S25 | * N/A, not novel |
| S313 | * N/A, not novel |
| S321 | * Phosphorylation at S321 occurs in response to infection by Yersinia enterocolotica by p38a/MK2 kinase(Dondelinger et al., 2017; Menon et al., 2017). * Phosphorylation at S321 by TAK1 prevents cell death induced by TNF(Geng et al., 2017; Jaco et al., 2017). |
| S415 | * N/A, not novel |
| S595 | * N/A, not novel |
| K20 | * N/A, not novel |
| K307 | * N/A, not novel |
| K429 | * Novel, no reference found |
| K612 | * N/A, not novel |
| K627 | * N/A, not novel |
| **RIPK3** | |
| S173 | * Novel, no reference found |
| S177 | * Novel, no reference found |
| S232 | * Phosphorylation at S232 is required for necrosome activation(Chen et al., 2013; Sun et al., 2012) |
| S254 | * Novel, no reference found |
| S321 | * N/A, not novel |
| T374 | * N/A, not novel |
| S380 | * N/A, not novel |
| T386 | * Novel, no reference found |
| T392 | * Novel, no reference found |
| T398 | * Novel, no reference found |
| T399 | * N/A, not novel |
| T407 | * Novel, no reference found |
| K145 | * Novel, no reference found |
| K230 | * Novel, no reference found |
| K298 | * Novel, no reference found |
| K359 | * Choi et al.(Choi et al., 2018) reported ubiquitylation of human K363 by PELI1 leading to RIP3K degradation |
| **PELI1** | |
| K162 | * N/A, not novel |
| K169 | * N/A, not novel |
| K202 | * K202 is one of five sites reported to be sumoylated *in vitro* and in cell extracts(Kim et al., 2011) |
| **MK08/JNK1** | |
| T183, Y185 | * Dérijard et al.(Dérijard et al., 1994, 1995) identified T183 and Y185 phosphorylation is required for JNK1 activation |
| S377 | * N/A, not novel |
| **JUNB** | |
| S23 | * Bakiri et al.(Bakiri et al., 2000) reported S23 phosphorylation in mitosis |
| T104 | * Phosphorylation of T104 regulates IL-4 expression in Th2 cells(Li et al., 1999) |
| S117 | * N/A, not novel |
| S234 | * N/A, not novel |
| S248, T252, S256 | * Phosphorylation of these residues by GSK3 leads to degradation of JunB in SCF-dependent manner in G2 phase of the cell cycle(Lee et al., 2013; Pérez-Benavente et al., 2013) |
| K36 | * N/A, not novel |
| K237 | * N/A, not novel |
| K322 | * N/A, not novel |
| **DDX58/RIG-I** | |
| K256 | * Novel, no reference found |
| K257 | * N/A, not novel |
| K259 | * N/A, not novel |
| K456 | * N/A, not novel |
| K645 | * N/A, not novel |
| **MAVS** | |
| S179 | * N/A, not novel |
| S186 | * N/A, not novel |
| S220 | * N/A, not novel |
| T222 | * N/A, not novel |
| Y332 | * Novel, no reference found |
| S384 | * N/A, not novel |
| **NOD2** | |
| No sites reported in our study. |  |
| **CGAS** | |
| S34 | * N/A, not novel |
| K55 | * Novel, no reference found |
| K486 | * N/A, not novel |
| **STING** | |
| No sites reported in our study. | ­ |
| **XIAP** | |
| S346 | * N/A, not novel |
| S429 | * Phosphorylation at S429 reported as a response to viral infection by Nakhaei et al.(Nakhaei et al., 2012). |
| K31 | * N/A, not novel |
| K208 | * N/A, not novel |
| K296 | * N/A, not novel |
| K357 | * N/A, not novel |
| **RIPK2** | |
| S183 | * Novel, no reference found |
| S364 | * N/A, not novel |
| S373 | * N/A, not novel |
| S381 | * Novel, no reference found |
| S414 | * N/A, not novel |
| K369 | * Novel, no reference found |
| **TRAF3** | |
| K334 | * N/A, not novel |
| K368 | * N/A, not novel |
| K512 | * N/A, not novel |
| **TRAF6** | |
| No sites reported in our study. |  |
| **MYD88** | |
| S136 | * Novel, no reference found |
| K127 | * N/A, not novel |
| K250 | * N/A, not novel |
| K256 | * N/A, not novel |
| K262 | * N/A, not novel |
| K291 | * N/A, not novel |
| **IRAK1** | |
| S185 | * N/A, not novel |
| K371 | * N/A, not novel |
| K397 | * N/A, not novel |
| **IRAK2** | |
| S136 | * N/A, not novel |
| T140 | * N/A, not novel |
| S168 | * N/A, not novel |
| S175 | * Novel, no reference found |
| T587 | * Novel, no reference found |
| S616 | * Novel, no reference found |
| **IRAK3** | |
| K60 | * Novel, no reference found |
| K163 | * Novel, no reference found |
| K392 | * N/A, not novel |
| **IRAK4** | |
| T133 | * Novel, no reference found |
| S134 | * Novel, no reference found |
| S152 | * N/A, not novel |
| S175\_S186 | * Novel, no reference found |
| **TBK1** | |
| S509 | * Novel, no reference found |
| S511 | * N/A, not novel |
| S716 | * N/A, not novel |
| **IRF3** | |
| Y107 | * N/A, not novel |
| S123 | * MAPK mediates phosphorylation at S123 during anti-viral response(Schmid et al., 2014; Wang et al., 2014) |
| T126 | * Novel, no reference found |
| S130 | * Novel, no reference found |
| S131 | * N/A, not novel |
| S135 | * S135 is phosphorylated by DNA-PK during viral response(Karpova et al., 2002) |
| S378, S379, S388, S394 | * Phosphorylation of this patch by multiple kinases including IKK and TBK1 is critical for triggering virus-induced activation of IRF3-driven gene expression(Mori et al., 2004; Panne et al., 2007; Yoneyama et al., 1998) |
| K70 | * Contributes to IRF3 regulation by sumoylation and ubiquitination(Ran et al., 2011) |
| **IRF7** | |
| S227 | * Novel, no reference found |
| T277 | * Novel, no reference found |
| **TLR2** | |
| No sites reported in our study. |  |
| **TLR4** | |
| K692 | * Novel, no reference found |
| **IFIT1** | |
| S272 | * Novel, no reference found |
| S296 | * Novel, no reference found |
| K89 | * Novel, no reference found |
| K117 | * Novel, no reference found |
| K123 | * Novel, no reference found |
| K406 | * Novel, no reference found |
| K451 | * Novel, no reference found |
| **IFIT2** | |
| K41 | * Novel, no reference found |
| K61 | * Novel, no reference found |
| K126 | * N/A, not novel |
| K158 | * Novel, no reference found |
| K163 | * N/A, not novel |
| K239 | * N/A, not novel |
| K291 | * Novel, no reference found |
| K357 | * N/A, not novel |
| **IFIT3** | |
| S327 | * Novel, no reference found |
| S333 | * Novel, no reference found |
| K189 | * N/A, not novel |
| K236 | * N/A, not novel |
| K246 | * Novel, no reference found |
| K252 | * Novel, no reference found |
| K266 | * Novel, no reference found |
| K396 | * Novel, no reference found |
| **ISG15** | |
| K30 | * Novel, no reference found |
| K35 | * N/A, not novel |
| K141 | * N/A, not novel |
| K148 | * N/A, not novel |
| **OASL1** | |
| No sites reported in our study. |  |
| **GBP1** | |
| K372 | * N/A, not novel |
| **GBP2** | |
| K389 | * N/A, not novel |
| K396 | * N/A, not novel |
| K444 | * N/A, not novel |
| K551 | * N/A, not novel |
| **GBP5** | |
| K279 | * Novel, no reference found |

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