Abstract

We recently reported that the ER stress kinase PERK regulates ER-mitochondria appositions and ER–plasma membrane (ER-PM) contact sites, independent of its canonical role in the unfolded protein response. PERK regulation of ER-PM contacts was revealed by a proximity biotinylation (BioID) approach and involved a dynamic PERK–Filamin A interaction supporting the formation of ER-PM contacts by actin-cytoskeleton remodeling in response to depletion of ER-Ca\(^{2+}\) stores. In this report, we further interrogated the PERK BioID interactome by validating through co-IP experiments the interaction between PERK and two proteins involved in Ca\(^{2+}\) handling and ER-mitochondria contact sites. These included the vesicle associated membrane (VAMP)-associated proteins (VAPA/B) and the main ER Ca\(^{2+}\) pump sarcoplasmic/endoplasmic reticulum Ca\(^{2+}\)-ATPase 2 (SERCA2). These data identify new putative PERK interacting proteins with a crucial role in membrane contact sites and Ca\(^{2+}\) signaling further supporting the uncanonical role of PERK in Ca\(^{2+}\) signaling through membrane contact sites (MCSs).

Keywords

cell biology, endoplasmic reticulum, ER stress, sarcoplasmic/endoplasmic reticulum Ca\(^{2+}\)-ATPase (SERCA), mitochondrial-associated membrane (MAM)

Introduction

The endoplasmic reticulum (ER) is a major cytoplasmic organelle that is involved in the synthesis and folding of proteins. However, when the ER can no longer match cellular protein folding demands, the resulting accumulation of unfolded proteins can trigger a cellular stress response known as the unfolded protein response (UPR) (Ron & Walter, 2007). The UPR is a conserved signaling pathway that activates transcription factors and translates unfolded proteins to restore ER homeostasis. One of the three mediators of the UPR is the ER stress kinase PKR-like endoplasmic reticulum kinase (PERK). PERK activation leads to the phosphorylation and activation of eukaryotic translation initiation factor 2α (eIF2α), which in turn inhibits translation of new proteins and promotes the expression of genes that are involved in ER homeostasis.

PERK has been implicated in the regulation of ER-mitochondria contact sites (MCSs) and ER–plasma membrane (PM) contact sites. PERK activation has been shown to induce ER-mitochondria appositions, which are essential for the maintenance of ER homeostasis. PERK activation has also been linked to the regulation of ER-Ca\(^{2+}\) stores, which are crucial for the regulation of Ca\(^{2+}\) signaling in the cell. PERK regulation of ER-Ca\(^{2+}\) stores has been shown to involve the inhibition of the ER Ca\(^{2+}\) pump, SERCA2, and the recruitment of Filamin A to the ER-mitochondria contact sites.

In this study, we further investigated the PERK interactome by validating through co-IP experiments the interaction between PERK and two proteins involved in Ca\(^{2+}\) handling and ER-mitochondria contact sites. These included the vesicle associated membrane (VAMP)-associated proteins (VAPA/B) and SERCA2. These data identify new putative PERK interacting proteins with crucial roles in membrane contact sites and Ca\(^{2+}\) signaling, further supporting the uncanonical role of PERK in Ca\(^{2+}\) signaling through membrane contact sites (MCSs).
proximity biotinylation (BioID) screen, using the promiscuous luminal domain and canonical ER stress, instead of being the activation of PERK can occur independently of its ER to the mitochondria. More recently, we showed that aids apoptotic cell death by the transfer of ROS signals from the cytosol to the mitochondria (Ron & Walter, 2007). In our previous studies (van Vliet et al., 2017), we uncovered that independent of its UPR function pause and giving the ER folding machinery time to deal with its protein burden (Ron & Walter, 2007).

To uncover the roles of PERK we carried out an unbiased PERK Proximity Interactome analysis. We further conducted IP/Co-IP analysis, which revealed the cytoskeletal protein Filamin A (FLNA) as a novel PERK interactor. The Ca²⁺-mediated PERK-FLNA axis was found to be required to support the formation of ER-PM contacts and store-operated Ca²⁺ entry (SOCE) (van Vliet et al., 2017). These findings support the formation of ER-PM contacts. Given the role of PERK in modulating ER homeostasis and its involvement in the formation of ER-PM contacts, we were interested in determining whether PERK interacts with proteins with a known tethering role and/or with a releasable ion in the ER. PERK is in an important mediator of the physical interaction between PERK and sarcoplasmic/endoplasmic reticulum Ca ATPase 2 (SERCA2) and VAPA/B, indicating that both proteins might interact with PERK and determine the regulation of membrane contact sites (MCSs). The isoforms VAPA and B are members of a small VAP protein family and have broadly similar structures and functions in vivo and in vitro. Missed VAPs are effects that are critical in the formation of membrane protein domains that are critical for the function of proteins in the endoplasmic reticulum (ER). They play a role in the formation of ER-mitochondria and indirectly ER-PM contacts, including protein tyrosine phosphatase interacting protein 51 (PTPIP51), StAR Related Lipid Transfer Domain Containing protein (STARD13) and Drosophila protein (Drosophila), among others (Alpy et al., 2013; De Vos et al., 2012; Dong et al., 2016; Wyles et al., 2002). VAPB is an important mediator of our approach, two of these groups are linked to PERK (Figure 1A and B).

In our previous studies (van Vliet et al., 2017; Verfaillie et al., 2012), we reported that PERK-BirA was expressed in HEK293-T cells and showed the expected ER localization (van Vliet et al., 2017). Our BioID analysis showed that PERK-BirA protein hits identified by LC-MS/MS in the streptavidin pull-down from PERK-BirA-transfected cells and not from mock-transfected cells treated in the same way (50 µM biotin for 24 h), as a control. Only biotinylated transfected parental HEK293-T cells treated in the same way were considered as putative interaction partners. Table 1 shows a list of PERK interaction partners. The table includes VAPA and VAPB, indicating that both proteins might interact with PERK. Because VAPA has been shown to be required for tethering (syntaxin 5, coatomer subunits), proteins involved in protein sorting (ERGIC-53), proteins involved in vesicle trafficking (TOM70, Sorting nexin 2 (SNX2)), actin cytoskeleton remodelling (syntaxin 5, coatomer subunits), proteins responsible for tethering and lipid trafficking (syntaxin 5, coatomer subunits), proteins involved in membrane contact sites (VAPA/B, FAPP1/2), PARK-associated Lethal Domain Containing protein (PARKAD), STARD3, and accessory protein (APAT) (Figure 1A and B).

The PERK Proximity Interactome

Table 1. PERK interaction partners. The table shows a list of PERK interaction partners and confirmed our observation that PERK is involved in the formation of ER-PM contacts. Interestingly, PERK has been linked recently with mitochondrial contact sites, including protein tyrosine phosphatase interacting protein 51 (PTPIP51), StAR Related Lipid Transfer Domain Containing protein (STARD13) and Drosophila protein (Drosophila) (Alpy et al., 2013; De Vos et al., 2012; Dong et al., 2016; Wyles et al., 2002). VAPB is an important mediator of our approach, two of these groups are linked to PERK (Figure 1A and B).

Results and Discussion

For these interaction partners, PERK kinase activity is dispensable. We generated a C-terminally tagged PERK-BirA protein construct (*), which was well expressed in HEK293-T cells and showed the expected ER localization. To match the original study reporting BioID (Roux et al., 2012), we uncovered that independent of its UPR function, PERK moonlights at the ER-mitochondria contacts and is activated upon ER stress (Ron & Walter, 2007). In our previous studies (van Vliet et al., 2017; Verfaillie et al., 2012), we showed that independent of its UPR function, PERK moonlights at the ER-mitochondria contacts and is activated upon ER stress (Ron & Walter, 2007).

However, many hits uncovered through our BioID experiment and the regulation of membrane contact sites (MCSs). The isoforms VAPA and B are members of a small VAP protein family and have broadly similar structures and functions in vivo and in vitro. Missed VAPs are effects that are critical in the formation of membrane protein domains that are critical for the function of proteins in the endoplasmic reticulum (ER). They play a role in the formation of ER-mitochondria and indirectly ER-PM contacts, including protein tyrosine phosphatase interacting protein 51 (PTPIP51), StAR Related Lipid Transfer Domain Containing protein (STARD13) and Drosophila protein (Drosophila), among others (Alpy et al., 2013; De Vos et al., 2012; Dong et al., 2016; Wyles et al., 2002). VAPB is an important mediator of our approach, two of these groups are linked to PERK (Figure 1A and B).

In our previous studies (van Vliet et al., 2017; Verfaillie et al., 2012), we reported that PERK-BirA was expressed in HEK293-T cells and showed the expected ER localization (van Vliet et al., 2017). Our BioID analysis showed that PERK-BirA protein hits identified by LC-MS/MS in the streptavidin pull-down from PERK-BirA-transfected cells and not from mock-transfected cells were taken into consideration as putative interaction partners. Table 1 shows a list of PERK interaction partners. The table includes VAPA and VAPB, indicating that both proteins might interact with PERK. Because VAPA has been shown to be required for tethering (syntaxin 5, coatomer subunits), proteins involved in protein sorting (ERGIC-53), proteins involved in vesicle trafficking (TOM70, Sorting nexin 2 (SNX2)), actin cytoskeleton remodelling (syntaxin 5, coatomer subunits), proteins responsible for tethering and lipid trafficking (syntaxin 5, coatomer subunits), proteins involved in membrane contact sites (VAPA/B, FAPP1/2), PARK-associated Lethal Domain Containing protein (PARKAD), STARD3, and accessory protein (APAT) (Figure 1A and B).

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Table 1. List of identified proteins (Scaffold, FDR < 1%) resulting from the BioID interactome screen using PERK-BirA as bait. Protein hits were only detected using PERK-BirA as bait and not in control. Parental cells are shaded in yellow. Relative quantification of proteins is based on spectral counts (‘Total spectra’). Only proteins with atleast 2 exclusive unique peptides per protein are listed.

| Identified proteins (276) | Accession number | Alternate ID | Molecular weight | Quantitative value (total spectra) PERK-BirA | Exclusive unique peptide count PERK-BirA | Quantitative value (total spectra) Control | Exclusive unique peptide count Control | Protein identification probability PERK-BirA | Protein identification probability Control |
|--------------------------|------------------|--------------|-------------------|-----------------------------------------------|-------------------------------------------|------------------------------------------|------------------------------------------|---------------------------------------------|---------------------------------------------|
| Eukaryotic translation initiation factor 2-alpha kinase 3 OS = Homo sapiens OX = 9606 GN = EIF2AK3 PE = 1 SV = 3 | Q9NZJ5 | EIF2AK3 | 125 kDa | 415 | 70 | 0 | 0 | 100% | 0 |
| Filamin-A OS = Homo sapiens OX = 9606 GN = FLNA PE = 1 SV = 4 | P21333 | FLNA | 281 kDa | 94 | 66 | 0 | 0 | 100% | 0 |
| Coatomer subunit gamma-2 OS = Homo sapiens OX = 9606 GN = COPG2 PE = 1 SV = 1 | Q9UBF2 | COPG2 | 98 kDa | 40 | 26 | 0 | 0 | 100% | 0 |
| Lamina-associated polypeptide 2, isoforms beta/gamma OS = Homo sapiens OX = 9606 GN = TMPO PE = 1 SV = 2 | P42167 | TMPO | 51 kDa | 28 | 16 | 0 | 0 | 100% | 0 |
| Keratin, type I cytoskeletal 16 OS = Homo sapiens OX = 9606 GN = KRT16 PE = 1 SV = 4 | P08779 | KRT16 | 51 kDa | 26 | 4 | 0 | 0 | 100% | 0 |
| Kinectin OS = Homo sapiens OX = 9606 GN = KTN1 PE = 1 SV = 1 | Q86UP2 | KTN1 | 156 kDa | 24 | 23 | 0 | 0 | 100% | 0 |
| RuvB-like 1 OS = Homo sapiens OX = 9606 GN = RUVBL1 PE = 1 SV = 1 | Q9Y265 | RUVBL1 | 50 kDa | 20 | 13 | 0 | 0 | 100% | 0 |
| E3 SUMO-protein ligase RanBP2 OS = Homo sapiens OX = 9606 GN = RANBP2 PE = 1 SV = 2 | P49792 | RANBP2 | 358 kDa | 20 | 19 | 0 | 0 | 100% | 0 |
| 78 kDa glucose-regulated protein OS = Homo sapiens GN = HSPA5 PE = 1 SV = 2 | P11021 | HSPA5 | 72 kDa | 16 | 13 | 0 | 0 | 100% | 0 |
| Double-strand break repair | P49959 | MRE11 | 81 kDa | 15 | 14 | 0 | 0 | 100% | 0 |

(continued)
| Identified proteins (276) | Accession number | Alternate ID | Molecular weight | Quantitative value (total spectra) PERK-BirA | Exclusive unique peptide count PERK-BirA | Quantitative value (total spectra) Control | Exclusive unique peptide count Control | Protein identification probability PERK-BirA | Protein identification probability Control |
|---------------------------|------------------|--------------|------------------|---------------------------------------------|----------------------------------------|--------------------------------------------|----------------------------------------|---------------------------------------------|---------------------------------------------|
| protein MRE11 OS = Homo sapiens OX = 9606 GN = MRE11 PE = 1 SV = 3 | Q7Z2W4 | ZC3HAV1 | 101 kDa | 14 | 10 | 0 | 0 | 100% | 0 |
| Zinc finger CCCH-type antiviral protein 1 OS = Homo sapiens OX = 9606 GN = ZC3HAV1 PE = 1 SV = 3 | Q14247 | CTTN | 62 kDa | 14 | 12 | 0 | 0 | 100% | 0 |
| Src substrate cortactin OS = Homo sapiens OX = 9606 GN = CTTN PE = 1 SV = 2 | P07814 | EPRS | 171 kDa | 12 | 11 | 0 | 0 | 100% | 0 |
| Bifunctional glutamate/proline--tRNA ligase OS = Homo sapiens OX = 9606 GN = EPRS PE = 1 SV = 5 | Q14739 | LBR | 71 kDa | 11 | 7 | 0 | 0 | 100% | 0 |
| Lamin-B receptor OS = Homo sapiens OX = 9606 GN = LBR PE = 1 SV = 2 | P37802 | TAGLN2 | 22 kDa | 10 | 7 | 0 | 0 | 100% | 0 |
| Transgelin-2 OS = Homo sapiens OX = 9606 GN = TAGLN2 PE = 1 SV = 3 | Q92616 | GCN1 | 293 kDa | 10 | 10 | 0 | 0 | 100% | 0 |
| eIF-2-alpha kinase activator GCN1 OS = Homo sapiens OX = 9606 GN = GCN1 PE = 1 SV = 6 | Q92575 | UBXN4 | 57 kDa | 10 | 6 | 0 | 0 | 100% | 0 |
| UBX domain-containing protein 4 OS = Homo sapiens OX = 9606 GN = UBXN4 PE = 1 SV = 2 | Q7KZF4 | SND1 | 102 kDa | 9 | 9 | 0 | 0 | 100% | 0 |
| Staphylococcal nuclease domain-containing protein 1 OS = Homo sapiens OX = 9606 GN = SND1 PE = 1 SV = 1 | Q9P0L0 | VAPA | 28 kDa | 8 | 4 | 0 | 0 | 100% | 0 |
Table 1. Continued.

| Identified proteins (276) | Accession number | Alternate ID | Molecular weight | Quantitative value (total spectra) | Exclusive unique peptide count | Protein identification probability |
|---------------------------|------------------|--------------|------------------|------------------------------------|------------------------------|-------------------------------|
| 9606 GN = VAPA PE = 1 SV = 3 | P16401 | HIST1H1B | 23 kDa | 7 | 3 | 0 | 100% | 0 |
| Histone H1.5 OS = Homo sapiens OX = 9606 GN = HIST1H1B PE = 1 SV = 3 | | | | | | | |
| Sodium/potassium-transporting ATPase subunit alpha-1 OS = Homo sapiens OX = 9606 GN = ATP1A1 PE = 1 SV = 1 | P05023 | ATP1A1 | 113 kDa | 7 | 7 | 0 | 0 | 100% | 0 |
| Eukaryotic translation initiation factor 5 OS = Homo sapiens OX = 9606 GN = EIF5 PE = 1 SV = 2 | P55010 | EIF5 | 49 kDa | 7 | 6 | 0 | 0 | 100% | 0 |
| Cytoskeleton-associated protein 4 OS = Homo sapiens OX = 9606 GN = CKAP4 PE = 1 SV = 2 | Q07065 | CKAP4 | 66 kDa | 7 | 7 | 0 | 0 | 100% | 0 |
| Protein ELYS OS = Homo sapiens OX = 9606 GN = AHCTF1 PE = 1 SV = 3 | Q8WYP5 | AHCTF1 | 253 kDa | 7 | 7 | 0 | 0 | 100% | 0 |
| MKL/myocardin-like protein 2 OS = Homo sapiens OX = 9606 GN = MKL2 PE = 1 SV = 3 | Q9ULH7 | MKL2 | 118 kDa | 7 | 7 | 0 | 0 | 100% | 0 |
| Neuroblast differentiation-associated protein AHNAK OS = Homo sapiens OX = 9606 GN = AHNAK PE = 1 SV = 2 | Q09666 | AHNAK | 629 kDa | 7 | 7 | 0 | 0 | 93% | 0 |
| Protein disulfide-isomerase A4 OS = Homo sapiens OX = 9606 GN = PDIA4 PE = 1 SV = 2 | P13667 | PDIA4 | 73 kDa | 6 | 5 | 0 | 0 | 100% | 0 |
| Coronin-IB OS = Homo sapiens OX = 9606 GN = CORO1B PE = 1 SV = 1 | Q9BR76 | CORO1B | 54 kDa | 6 | 6 | 0 | 0 | 100% | 0 |
| Splicing factor, proline- and | P23246 | SFPQ | 76 kDa | 6 | 4 | 0 | 0 | 100% | 0 |

(continued)
Table 1. Continued.

| Identified proteins (276) | Accession number | Alternate ID | Molecular weight | Quantitative value (total spectra) | Exclusive unique peptide count | Quantitative value (total spectra) | Exclusive unique peptide count | Protein identification probability | Protein identification probability |
|--------------------------|------------------|--------------|------------------|----------------------------------|-------------------------------|----------------------------------|-------------------------------|---------------------------------|---------------------------------|
| glutamine-rich OS = Homo sapiens OX = 9606 GN = SFPQ PE = 1 SV = 2 | P07737 | PFN1 | 15 kDa | 6 | 6 | 0 | 0 | 100% | 0 |
| Profilin-1 OS = Homo sapiens OX = 9606 GN = PFN1 PE = 1 SV = 2 | P78344 | EIF4G2 | 102 kDa | 6 | 6 | 0 | 0 | 100% | 0 |
| Eukaryotic translation initiation factor 4 gamma 2 OS = Homo sapiens OX = 9606 GN = EIF4G2 PE = 1 SV = 1 | Q96A33 | CCDC47 | 56 kDa | 6 | 6 | 0 | 0 | 100% | 0 |
| Coiled-coil domain-containing protein 47 OS = Homo sapiens OX = 9606 GN = CCDC47 PE = 1 SV = 1 | P14625 | HSP90B1 | 92 kDa | 6 | 6 | 0 | 0 | 100% | 0 |
| Endoplasmic reticulum-associated protein 90 beta 1 OS = Homo sapiens OX = 9606 GN = HSP90B1 PE = 1 SV = 1 | P23588 | EIF4B | 69 kDa | 6 | 6 | 0 | 0 | 100% | 0 |
| EIF4B OS = Homo sapiens OX = 9606 GN = EIF4B PE = 1 SV = 2 | P22234 | PAICS | 47 kDa | 6 | 5 | 0 | 0 | 100% | 0 |
| Multifunctional protein ADE2 OS = Homo sapiens OX = 9606 GN = PAICS PE = 1 SV = 3 | Q5JTV8 | TOR1AIP1 | 66 kDa | 6 | 6 | 0 | 0 | 100% | 0 |
| Torsin-1A-interacting protein 1 OS = Homo sapiens OX = 9606 GN = TOR1AIP1 PE = 1 SV = 2 | Q5VV42 | CDKAL1 | 65 kDa | 6 | 5 | 0 | 0 | 100% | 0 |
| Threonylcarbamoyladenosine tRNA methylthiotransferase OS = Homo sapiens OX = 9606 GN = CDKAL1 PE = 1 SV = 1 | P63244 | RACK1 | 35 kDa | 6 | 5 | 0 | 0 | 100% | 0 |
| Receptor of activated protein C kinase 1 OS = Homo sapiens | (continued) |
| Identified proteins (276) | Accession number | Alternate ID | Molecular weight | Quantitative value (total spectra) PERK-BirA | Exclusive unique peptide count PERK-BirA | Quantitative value (total spectra) Control | Exclusive unique peptide count Control | Protein identification probability PERK-BirA | Protein identification probability Control |
|-------------------------|------------------|--------------|------------------|-----------------------------------------------|------------------------------------------|-------------------------------------------|-------------------------------------------|---------------------------------------------|---------------------------------------------|
| Membrane-associated progesterone receptor component 2 OS = Homo sapiens OX = 9606 GN = PGRMC2 PE = 1 SV = 1 | O15173           | PGRMC2       | 24 kDa           | 5                                             | 3                                        | 0                                          | 0                                          | 100%                                        | 0                                          |
| Chromodomain-helicase-DNA-binding protein 4 OS = Homo sapiens OX = 9606 GN = CHD4 PE = 1 SV = 2 | Q14839           | CHD4         | 218 kDa          | 5                                             | 5                                        | 0                                          | 0                                          | 100%                                        | 0                                          |
| Afadin OS = Homo sapiens OX = 9606 GN = AFDN PE = 1 SV = 3 | P55196           | AFDN         | 207 kDa          | 5                                             | 5                                        | 0                                          | 0                                          | 100%                                        | 0                                          |
| Adapter molecule crk OS = Homo sapiens OX = 9606 GN = CRK PE = 1 SV = 2 | P46108           | CRK          | 34 kDa           | 5                                             | 5                                        | 0                                          | 0                                          | 100%                                        | 0                                          |
| Nucleophosmin OS = Homo sapiens OX = 9606 GN = NPM1 PE = 1 SV = 2 | P06748           | NPM1         | 33 kDa           | 5                                             | 5                                        | 0                                          | 0                                          | 100%                                        | 0                                          |
| Sarcoplasmic/endoplasmic reticulum calcium ATPase 2 OS = Homo sapiens OX = 9606 GN = ATP2A2 PE = 1 SV = 1 | P16615           | ATP2A2       | 115 kDa          | 5                                             | 5                                        | 0                                          | 0                                          | 100%                                        | 0                                          |
| Peroxiredoxin-4 OS = Homo sapiens OX = 9606 GN = PRDX4 PE = 1 SV = 1 | Q13162           | PRDX4        | 31 kDa           | 5                                             | 2                                        | 0                                          | 0                                          | 100%                                        | 0                                          |
| Eukaryotic translation initiation factor 4 gamma 1 OS = Homo sapiens OX = 9606 GN = EIF4G1 PE = 1 SV = 4 | Q04637           | EIF4G1       | 175 kDa          | 5                                             | 4                                        | 0                                          | 0                                          | 100%                                        | 0                                          |
| Cytokeleton-associated protein 5 OS = Homo sapiens OX = 9606 GN = CKAP5 PE = 1 SV = 3 | Q14008           | CKAP5        | 226 kDa          | 4                                             | 4                                        | 0                                          | 0                                          | 100%                                        | 0                                          |
| PEST proteolytic signal- | Q8WW12           | PCNP         | 19 kDa           | 4                                             | 2                                        | 0                                          | 0                                          | 98%                                         | 0                                          |

(continued)
| Identified proteins (276) | Accession number | Alternate ID | Molecular weight | Quantitative value (total spectra) PERK-BirA | Exclusive unique peptide count PERK-BirA | Quantitative value (total spectra) Control | Exclusive unique peptide count Control | Protein identification probability PERK-BirA | Protein identification probability Control |
|--------------------------|------------------|--------------|-----------------|------------------------------------------|--------------------------------------|-------------------------------------------|----------------------------------------|---------------------------------------------|---------------------------------------------|
| containing nuclear protein OS = Homo sapiens  | OS = Homo sapiens  | = OS = Homo sapiens  | = PCNP PE = 1  | = 2 |  |  |  |  |  |
| Desmoplakin OS = Homo sapiens  | P15924 | DSP | 332 kDa | 4 | 4 | 0 | 0 | 0 | 100% |
| Ubiquitin-like modifier-activating enzyme 1 OS = Homo sapiens  | P22314 | UBA1 | 118 kDa | 4 | 4 | 0 | 0 | 0 | 100% |
| Fatty aldehyde dehydrogenase OS = Homo sapiens  | P51648 | ALDH3A2 | 55 kDa | 4 | 4 | 0 | 0 | 0 | 100% |
| Creatine kinase B-type OS = Homo sapiens  | P12277 | CKB | 43 kDa | 4 | 4 | 0 | 0 | 0 | 100% |
| Syntaxin-5 OS = Homo sapiens  | Q13190 | STX5 | 40 kDa | 4 | 4 | 0 | 0 | 0 | 100% |
| Rab-like protein 3 OS = Homo sapiens  | Q5HYI8 | RABL3 | 26 kDa | 4 | 3 | 0 | 0 | 0 | 100% |
| Regulator of chromosome condensation OS = Homo sapiens  | P18754 | RCC1 | 45 kDa | 4 | 4 | 0 | 0 | 0 | 100% |
| Ran GTPase-activating protein 1 OS = Homo sapiens  | P46060 | RANGAP1 | 64 kDa | 4 | 4 | 0 | 0 | 0 | 100% |
| Synaptobrevin homolog YKT6 OS = Homo sapiens  | O15498 | YKT6 | 22 kDa | 4 | 3 | 0 | 0 | 0 | 100% |
| Cold shock domain-containing protein E1 OS = Homo sapiens  | O75534 | CSDE1 | 89 kDa | 4 | 4 | 0 | 0 | 0 | 100% |

(continued)
Table 1. Continued.

| Identified proteins (276) | Accession number | Alternate ID | Molecular weight | Quantitative value (total spectra) PERK-BirA | Exclusive unique peptide count PERK-BirA | Quantitative value (total spectra) Control | Exclusive unique peptide count Control | Protein identification probability PERK-BirA | Protein identification probability Control |
|--------------------------|------------------|--------------|------------------|---------------------------------------------|------------------------------------------|-------------------------------------------|---------------------------------------------|---------------------------------------------|---------------------------------------------|
| OX = 9606 GN = CSDE1 PE = 1 SV = 2 | Vesicle-associated membrane protein-associated protein B/C OS = Homo sapiens OX = 9606 GN = VAPB PE = 1 SV = 3 | O95292 | VAPB | 27 kDa | 4 | 2 | 0 | 0 | 99% | 0 |
| OX = 9606 GN = HDLBP PE = 1 SV = 2 | Vigilin OS = Homo sapiens OX = 9606 GN = HDLBP PE = 1 SV = 3 | Q00341 | HDLBP | 141 kDa | 4 | 4 | 0 | 0 | 99% | 0 |
| OX = 9606 GN = MAP4 PE = 1 SV = 3 | Microtubule-associated protein 4 OS = Homo sapiens OX = 9606 GN = MAP4 PE = 1 SV = 3 | P27816 | MAP4 | 121 kDa | 4 | 3 | 0 | 0 | 100% | 0 |
| OX = 9606 GN = TAF15 PE = 1 SV = 3 | TATA-binding protein-associated factor 2N OS = Homo sapiens OX = 9606 GN = TAF15 PE = 1 SV = 3 | Q92804 | TAF15 | 62 kDa | 3 | 2 | 0 | 0 | 84% | 0 |
| OX = 9606 GN = PPIA PE = 1 SV = 2 | Peptidyl-prolyl cis-trans isomerase A OS = Homo sapiens OX = 9606 GN = PPIA PE = 1 SV = 2 | P62937 | PPIA | 18 kDa | 3 | 3 | 0 | 0 | 100% | 0 |
| OX = 9606 GN = CAD PE = 1 SV = 3 | CAD protein OS = Homo sapiens OX = 9606 GN = CAD PE = 1 SV = 3 | P27708 | CAD | 243 kDa | 3 | 3 | 0 | 0 | 100% | 0 |
| OX = 9606 GN = SYAP1 PE = 1 SV = 1 | Synapse-associated protein 1 OS = Homo sapiens OX = 9606 GN = SYAP1 PE = 1 SV = 1 | Q96A49 | SYAP1 | 40 kDa | 3 | 3 | 0 | 0 | 100% | 0 |
| OX = 9606 GN = LRRC59 PE = 1 SV = 1 | Leucine-rich repeat-containing protein 59 OS = Homo sapiens OX = 9606 GN = LRRC59 PE = 1 SV = 1 | Q96AG4 | LRRC59 | 35 kDa | 3 | 3 | 0 | 0 | 100% | 0 |
| OX = 9606 GN = WWOX PE = 1 SV = 1 | WW domain-containing oxidoreductase OS = Homo sapiens OX = 9606 GN = WWOX PE = 1 SV = 1 | Q9NZC7 | WWOX | 47 kDa | 3 | 3 | 0 | 0 | 99% | 0 |
| OX = 9606 GN = PHGDH PE = 1 SV = 1 | D-3-phosphoglycerate | O43175 | PHGDH | 57 kDa | 3 | 3 | 0 | 0 | 100% | 0 |

(continued)
| Identified proteins (276) | Accession number | Alternate ID | Molecular weight | Quantitative value (total spectra) | Exclusive unique peptide count | Quantitative value (total spectra) | Exclusive unique peptide count | Protein identification probability | Protein identification probability |
|--------------------------|------------------|--------------|------------------|-----------------------------------|-------------------------------|----------------------------------|-------------------------------|-------------------------------|-------------------------------|
| dehydrogenase OS = Homo sapiens OX = 9606 GN = PHGDH PE = 1 SV = 4 | P23396 | RPS3 | 27 kDa | 3 | 3 | 0 | 0 | 100% | 0 |
| 40S ribosomal protein S3 OS = Homo sapiens OX = 9606 GN = RPS3 PE = 1 SV = 2 | P45880 | VDAC2 | 32 kDa | 3 | 3 | 0 | 0 | 100% | 0 |
| Voltage-dependent anion-selective channel protein 2 OS = Homo sapiens OX = 9606 GN = VDAC2 PE = 1 SV = 2 | Q9Y2J2 | EPB41L3 | 121 kDa | 3 | 3 | 0 | 0 | 100% | 0 |
| Band 4.1-like protein 3 OS = Homo sapiens OX = 9606 GN = EPB41L3 PE = 1 SV = 2 | Q9HDC5 | JPH1 | 72 kDa | 3 | 2 | 0 | 0 | 100% | 0 |
| Emerin OS = Homo sapiens OX = 9606 GN = EMD PE = 1 SV = 1 | P50402 | EMD | 29 kDa | 3 | 2 | 0 | 0 | 100% | 0 |
| Thioredoxin-dependent peroxide reductase, mitochondrial OS = Homo sapiens OX = 9606 GN = PRDX3 PE = 1 SV = 3 | P30048 | PRDX3 | 28 kDa | 3 | 3 | 0 | 0 | 100% | 0 |
| Eukaryotic translation initiation factor 5B OS = Homo sapiens OX = 9606 GN = EIF5B PE = 1 SV = 4 | O60841 | EIF5B | 139 kDa | 3 | 3 | 0 | 0 | 99% | 0 |
| Clathrin heavy chain 1 OS = Homo sapiens OX = 9606 GN = CLTC PE = 1 SV = 5 | Q00610 | CLTC | 192 kDa | 3 | 3 | 0 | 0 | 99% | 0 |
| Stromal interaction molecule 1 OS = Homo sapiens OX = 9606 GN = STIM1 PE = 1 SV = 3 | Q13586 | STIM1 | 77 kDa | 3 | 2 | 0 | 0 | 98% | 0 |
| Splicing factor 3B subunit 3 OS = Homo sapiens OX = 9606 GN = SF3B3 PE = 1 SV = 4 | Q15393 | SF3B3 | 136 kDa | 3 | 3 | 0 | 0 | 96% | 0 |

(continued)
| Identified proteins (276) | Accession number | Alternate ID | Molecular weight | Quantitative value (total spectra) PERK-BirA | Exclusive unique peptide count PERK-BirA | Quantitative value (total spectra) Control | Exclusive unique peptide count Control | Protein identification probability PERK-BirA | Protein identification probability Control |
|--------------------------|------------------|--------------|------------------|-----------------------------------------------|------------------------------------------|---------------------------------------------|------------------------------------------|-----------------------------------------------|-----------------------------------------------|
| Nuclear migration protein nudC | Q9Y266 | NUDC | 38 kDa | 3 | 3 | 0 | 0 | 93% | 0 |
| OS = Homo sapiens OX = 9606 GN = NUDC PE = 1 SV = 1 |
| Proliferation marker protein Ki-67 | P46013 | MKI67 | 359 kDa | 3 | 2 | 0 | 0 | 84% | 0 |
| OS = Homo sapiens OX = 9606 GN = MKI67 PE = 1 SV = 2 |
| Chloride channel CLIC-like protein 1 | Q96S66 | CLCC1 | 62 kDa | 3 | 3 | 0 | 0 | 99% | 0 |
| OS = Homo sapiens OX = 9606 GN = CLCC1 PE = 1 SV = 1 |
| Far upstream element-binding protein 2 | Q92945 | KHSRP | 73 kDa | 3 | 3 | 0 | 0 | 96% | 0 |
| OS = Homo sapiens OX = 9606 GN = KHSRP PE = 1 SV = 4 |
| Clathrin interactor 1 | Q14677 | CLINT1 | 68 kDa | 3 | 3 | 0 | 0 | 91% | 0 |
| OS = Homo sapiens OX = 9606 GN = CLINT1 PE = 1 SV = 1 |
| Eukaryotic translation initiation factor 2A | Q9BY44 | EIF2A | 65 kDa | 3 | 3 | 0 | 0 | 61% | 0 |
| OS = Homo sapiens OX = 9606 GN = EIF2A PE = 1 SV = 3 |
| Junction plakoglobin | P14923 | JUP | 82 kDa | 3 | 3 | 0 | 0 | 40% | 0 |
| OS = Homo sapiens OX = 9606 GN = JUP PE = 1 SV = 3 |
| Pre-mRNA-splicing factor ATP-dependent RNA helicase DHX15 | O43143 | DHX15 | 91 kDa | 2 | 2 | 0 | 0 | 100% | 0 |
| OS = Homo sapiens OX = 9606 GN = DHX15 PE = 1 SV = 2 |
| T-complex protein 1 subunit zeta | P40227 | CCT6A | 58 kDa | 2 | 2 | 0 | 0 | 100% | 0 |
| OS = Homo sapiens OX = 9606 GN = CCT6A PE = 1 SV = 3 |
| Cytoplasmic dynein 1 heavy chain 1 | Q14204 | DYNC1H1 | 532 kDa | 2 | 2 | 0 | 0 | 100% | 0 |
| OS = Homo sapiens |

(continued)
| Identified proteins (276)                                                                 | Accession number | Alternate ID | Molecular weight | Quantitative value (total spectra) PERK-BirA | Exclusive unique peptide count PERK-BirA | Quantitative value (total spectra) Control | Exclusive unique peptide count Control | Protein identification probability PERK-BirA | Protein identification probability Control |
|------------------------------------------------------------------------------------------|------------------|--------------|------------------|----------------------------------------------|------------------------------------------|--------------------------------------------|-------------------------------------------|-----------------------------------------------|-----------------------------------------------|
| 60S ribosomal protein L15 OS = Homo sapiens OX = 9606 GN = RPL15 PE = 1 SV = 2           | P61313           | RPL15        | 24 kDa           | 2                                            | 2                                        | 0                                          | 0                                         | 100%                                          | 0                                             |
| Dolichyl-diphosphooligosaccharide–protein glycosyltransferase subunit STT3B OS = Homo sapiens OX = 9606 GN = STT3B PE = 1 SV = 1 | Q8TCJ2           | STT3B        | 94 kDa           | 2                                            | 2                                        | 0                                          | 0                                         | 100%                                          | 0                                             |
| Protein SGT1 homolog OS = Homo sapiens OX = 9606 GN = SUGT1 PE = 1 SV = 1              | Q9Y2Z0           | SUGT1        | 41 kDa           | 2                                            | 2                                        | 0                                          | 0                                         | 100%                                          | 0                                             |
| Protein 4.1 OS = Homo sapiens OX = 9606 GN = EPB41 PE = 1 SV = 4                       | P11171           | EPB41        | 97 kDa           | 2                                            | 2                                        | 0                                          | 0                                         | 100%                                          | 0                                             |
| Heterogeneous nuclear ribonucleoprotein D0 OS = Homo sapiens OX = 9606 GN = HNRNPD PE = 1 SV = 1 | Q14103           | HNRNPD       | 38 kDa           | 2                                            | 2                                        | 0                                          | 0                                         | 100%                                          | 0                                             |
| Chloride intracellular channel protein 1 OS = Homo sapiens OX = 9606 GN = CLIC1 PE = 1 SV = 4 | O00299           | CLIC1        | 27 kDa           | 2                                            | 2                                        | 0                                          | 0                                         | 100%                                          | 0                                             |
| Signal recognition particle subunit SRP68 OS = Homo sapiens OX = 9606 GN = SRP68 PE = 1 SV = 2 | Q9UHB9           | SRP68        | 71 kDa           | 2                                            | 2                                        | 0                                          | 0                                         | 100%                                          | 0                                             |
| Signal recognition particle 54 kDa protein OS = Homo sapiens OX = 9606 GN = SRP54 PE = 1 SV = 1 | P61011           | SRP54        | 56 kDa           | 2                                            | 2                                        | 0                                          | 0                                         | 100%                                          | 0                                             |
| Polyadenylate-binding protein 1 OS = Homo sapiens OX = 9606 GN = PABPC1 PE = 1 SV = 2   | P11940           | PABPC1       | 71 kDa           | 2                                            | 2                                        | 0                                          | 0                                         | 100%                                          | 0                                             |

(continued)
| Identified proteins (276) | Accession number | Alternate ID | Molecular weight | Quantitative value (total spectra) | Exclusive unique peptide count | Quantitative value (total spectra) | Exclusive unique peptide count | Protein identification probability | Protein identification probability |
|--------------------------|------------------|--------------|------------------|-----------------------------------|-------------------------------|-----------------------------------|-------------------------------|----------------------------------|----------------------------------|
| T-complex protein 1 subunit epsilon | P48643 | CCT5 | 60 kDa | 2 | 2 | 0 | 0 | 100% | 0 |
| C-1-tetrahydrofolate synthase, cytoplasmic | P11586 | MTHFD1 | 102 kDa | 2 | 2 | 0 | 0 | 100% | 0 |
| Voltage-dependent anion-selective channel protein 3 | Q9Y277 | VDAC3 | 31 kDa | 2 | 2 | 0 | 0 | 100% | 0 |
| RNA-binding protein 26 | Q5T8P6 | RBM26 | 114 kDa | 2 | 2 | 0 | 0 | 99% | 0 |
| Ran-binding protein 3 | Q9H6Z4 | RANBP3 | 60 kDa | 2 | 2 | 0 | 0 | 99% | 0 |
| 60S ribosomal protein L10 | P27635 | RPL10 | 25 kDa | 2 | 2 | 0 | 0 | 99% | 0 |
| Protein RCC2 | Q9P258 | RCC2 | 56 kDa | 2 | 2 | 0 | 0 | 98% | 0 |
| Extended synaptotagmin-1 | Q9BSJ8 | ESYT1 | 123 kDa | 2 | 2 | 0 | 0 | 97% | 0 |
| PC4 and SFRS1-interacting protein | O75475 | PSIP1 | 60 kDa | 2 | 2 | 0 | 0 | 94% | 0 |
| SAFB-like transcription modulator | Q9NWH9 | SLTM | 117 kDa | 2 | 2 | 0 | 0 | 92% | 0 |
| Probable rRNA-processing protein EBP2 | Q99848 | EBNA1BP2 | 35 kDa | 2 | 2 | 0 | 0 | 80% | 0 |
| Identified proteins (276) | Accession number | Alternate ID | Molecular weight | Quantitative value (total spectra) PERK-BirA | Exclusive unique peptide count PERK-BirA | Quantitative value (total spectra) Control | Exclusive unique peptide count Control | Protein identification probability PERK-BirA | Protein identification probability Control |
|--------------------------|------------------|--------------|------------------|--------------------------------------------|----------------------------------------|--------------------------------------------|------------------------------------------|--------------------------------------------|--------------------------------------------|
| Cysteine and histidine-rich domain-containing protein 1 OS = Homo sapiens OX = 9606 GN = CHORDC1 PE = 1 SV = 2 | Q9UHD1 | CHORDC1 | 37 kDa | 2 | 2 | 0 | 0 | 79% | 0 |
| ATP-dependent RNA helicase DDX39A OS = Homo sapiens OX = 9606 GN = DDX39A PE = 1 SV = 2 | O00148 (+1) | DDX39A | 49 kDa | 2 | 2 | 0 | 0 | 100% | 0 |
| Heterogeneous nuclear ribonucleoprotein H3 OS = Homo sapiens OX = 9606 GN = HNRNPH3 PE = 1 SV = 2 | P31942 | HNRNPH3 | 37 kDa | 2 | 2 | 0 | 0 | 100% | 0 |
| Peroxisomal multifunctional enzyme type 2 OS = Homo sapiens OX = 9606 GN = HSD17B4 PE = 1 SV = 3 | P51659 | HSD17B4 | 80 kDa | 2 | 2 | 0 | 0 | 98% | 0 |
| Eukaryotic translation initiation factor 3 subunit D OS = Homo sapiens OX = 9606 GN = EIF3D PE = 1 SV = 1 | O15371 | EIF3D | 64 kDa | 2 | 2 | 0 | 0 | 96% | 0 |
| Tyrosine-protein phosphatase non-receptor type 1 OS = Homo sapiens OX = 9606 GN = PTPN1 PE = 1 SV = 1 | P18031 | PTPN1 | 50 kDa | 2 | 2 | 0 | 0 | 92% | 0 |
| Jupiter microtubule associated homolog 2 OS = Homo sapiens OX = 9606 GN = JPT2 PE = 1 SV = 1 | Q9H910 | JPT2 | 20 kDa | 2 | 2 | 0 | 0 | 90% | 0 |
| U5 small nuclear ribonucleoprotein 200 kDa helicase OS = Homo sapiens OX = 9606 GN = SNRNP200 PE = 1 SV = 2 | O75643 | SNRNP200 | 245 kDa | 2 | 2 | 0 | 0 | 89% | 0 |
| PDZ and LIM domain protein 5 | Q9HC4 | PDLIM5 | 64 kDa | 2 | 2 | 0 | 0 | 86% | 0 |

(continued)
| Identified proteins (276) | Accession number | Alternate ID | Molecular weight | Quantitative value (total spectra) PERK-BirA | Exclusive unique peptide count PERK-BirA | Quantitative value (total spectra) Control | Exclusive unique peptide count Control | Protein identification probability PERK-BirA | Protein identification probability Control |
|--------------------------|------------------|--------------|------------------|---------------------------------------------|------------------------------------------|--------------------------------------------|-------------------------------------------|-------------------------------------------|-------------------------------------------|
| OS = Homo sapiens OX = 9606 GN = PDLIM5 PE = 1 SV = 5 | Coatomer subunit alpha OS = Homo sapiens OX = 9606 GN = COPA PE = 1 SV = 2 | P53621 | COPA | 138 kDa | 2 | 2 | 0 | 0 | 86% | 0 |
| Activator of 90 kDa heat shock protein ATPase homolog 1 OS = Homo sapiens OX = 9606 GN = AHSA1 PE = 1 SV = 1 | Asparagine synthetase [glutamine-hydrolyzing] OS = Homo sapiens OX = 9606 GN = ASNS PE = 1 SV = 4 | P08243 | ASNS | 64 kDa | 2 | 2 | 0 | 0 | 69% | 0 |
| Transitional endoplasmic reticulum ATPase OS = Homo sapiens OX = 9606 GN = VCP PE = 1 SV = 4 | RNA cytidine acetyltransferase OS = Homo sapiens OX = 9606 GN = NAT10 PE = 1 SV = 2 | Q9H0A0 | NAT10 | 116 kDa | 2 | 2 | 0 | 0 | 54% | 0 |
| Protein arginine N-methyltransferase 5 OS = Homo sapiens OX = 9606 GN = PRMT5 PE = 1 SV = 4 | 60S ribosomal protein L38 OS = Homo sapiens OX = 9606 GN = RPL38 PE = 1 SV = 2 | P63173 | RPL38 | 8 kDa | 2 | 2 | 0 | 0 | 37% | 0 |
| Angiomotin OS = Homo sapiens OX = 9606 GN = AMOT PE = 1 SV = 1 | Segment polarity protein dishevelled homolog DVL-2 OS = Homo sapiens OX = 9606 GN = DVL2 PE = 1 SV = 1 | Q4VCS5 | AMOT | 118 kDa | 2 | 2 | 0 | 0 | 29% | 0 |
| | | O14641 | DVL2 | 79 kDa | 2 | 2 | 0 | 0 | 21% | 0 |

(continued)
| Identified proteins (276)                                                                 | Accession number | Alternate ID | Molecular weight | Quantitative value (total spectra) PERK-BirA | Exclusive unique peptide count PERK-BirA | Quantitative value (total spectra) Control | Exclusive unique peptide count Control | Protein identification probability PERK-BirA | Protein identification probability Control |
|------------------------------------------------------------------------------------------|------------------|--------------|------------------|---------------------------------------------|------------------------------------------|-------------------------------------------|------------------------------------------|---------------------------------------------|---------------------------------------------|
| DDRGK domain-containing protein 1 OS = Homo sapiens OX = 9606 GN = DDRGK1 PE = 1 SV = 2   | Q96HY6           | DDRGK1       | 36 kDa           | 2                                           | 2                                        | 0                                         | 0                                        | 41%                                         | 0                                           |
| Calponin-3 OS = Homo sapiens OX = 9606 GN = CNN3 PE = 1 SV = 1                           | Q15417           | CNN3         | 36 kDa           | 2                                           | 2                                        | 0                                         | 0                                        | 19%                                         | 0                                           |
| Synaptosomal-associated protein 29 OS = Homo sapiens OX = 9606 GN = SNAP29 PE = 1 SV = 1 | O95721           | SNAP29       | 29 kDa           | 2                                           | 2                                        | 0                                         | 0                                        | 16%                                         | 0                                           |
| T-complex protein 1 subunit theta OS = Homo sapiens OX = 9606 GN = CCT8 PE = 1 SV = 4   | P50990           | CCT8         | 60 kDa           | 58                                          | 32                                       | 1                                         | 1                                        | 100%                                        | 55%                                         |
| Fatty acid synthase OS = Homo sapiens OX = 9606 GN = FASN PE = 1 SV = 3                 | P49327           | FASN         | 273 kDa          | 32                                          | 27                                       | 1                                         | 1                                        | 100%                                        | 82%                                         |
| Protein LYRIC OS = Homo sapiens OX = 9606 GN = MTDH PE = 1 SV = 2                       | Q86UE4           | MTDH         | 64 kDa           | 24                                          | 15                                       | 1                                         | 1                                        | 100%                                        | 11%                                         |
| Plasminogen activator inhibitor 1 RNA-binding protein OS = Homo sapiens OX = 9606 GN = SERBP1 PE = 1 SV = 2 | Q8NC51           | SERBP1       | 45 kDa           | 12                                          | 8                                        | 1                                         | 1                                        | 100%                                        | 77%                                         |
| Ubiquitin-40S ribosomal protein S27a OS = Homo sapiens OX = 9606 GN = RPS27A PE = 1 SV = 2 | P62979           | RPS27A       | 18 kDa           | 16                                          | 7                                        | 1                                         | 1                                        | 100%                                        | 15%                                         |
| Heterogeneous nuclear ribonucleoprotein L OS = Homo sapiens OX = 9606 GN = HNRNPL PE = 1 SV = 2 | P14866           | HNRNPL       | 64 kDa           | 9                                           | 9                                        | 1                                         | 1                                        | 100%                                        | 94%                                         |
| Poly(rC)-binding protein 1 OS = Homo sapiens OX = 9606 GN = PCBP1 PE = 1 SV = 2         | Q15365           | PCBP1        | 37 kDa           | 7                                           | 5                                        | 1                                         | 1                                        | 100%                                        | 98%                                         |
| Eukaryotic initiation factor 4A-I OS = Homo sapiens OX = 9606 GN = PCBP1 PE = 1 SV = 2 | P60842           | EIF4A1       | 46 kDa           | 6                                           | 6                                        | 1                                         | 1                                        | 100%                                        | 81%                                         |

(continued)
| Identified proteins (276) | Accession number | Alternate ID | Molecular weight | Quantitative value (total spectra) PERK-BirA | Exclusive unique peptide count PERK-BirA | Quantitative value (total spectra) Control | Exclusive unique peptide count Control | Protein identification probability PERK-BirA | Protein identification probability Control |
|--------------------------|------------------|--------------|------------------|-----------------------------------------------|------------------------------------------|---------------------------------------------|----------------------------------------|-------------------------------------------|---------------------------------------------|
| OS = Homo sapiens OX = 9606 GN = EIF4A1 PE = 1 SV = 1 | | | | | | | | | |
| Heterogeneous nuclear ribonucleoprotein A3 OS = Homo sapiens OX = 9606 GN = HNRNPA3 PE = 1 SV = 2 | P51991 | HNRNPA3 | 40 kDa | 5 | 5 | 1 | 1 | 100% | 98% |
| GTP-binding nuclear protein Ran OS = Homo sapiens OX = 9606 GN = RAN PE = 1 SV = 3 | P62826 | RAN | 24 kDa | 5 | 5 | 1 | 1 | 100% | 93% |
| ADP/ATP translocase 2 OS = Homo sapiens OX = 9606 GN = SLC25A5 PE = 1 SV = 7 | P05141 | SLC25A5 | 33 kDa | 4 | 4 | 1 | 1 | 100% | 92% |
| Splicing regulatory glutamine/lysine-rich protein 1 OS = Homo sapiens OX = 9606 GN = SREK1 PE = 1 SV = 1 | Q8WXA9 | SREK1 | 59 kDa | 4 | 4 | 1 | 1 | 100% | 47% |
| 60S ribosomal protein L12 OS = Homo sapiens OX = 9606 GN = RPL12 PE = 1 SV = 1 | P30050 | RPL12 | 18 kDa | 3 | 2 | 1 | 1 | 100% | 76% |
| Fructose-bisphosphate aldolase A OS = Homo sapiens OX = 9606 GN = ALDOA PE = 1 SV = 2 | P04075 | ALDOA | 39 kDa | 4 | 4 | 1 | 1 | 100% | 20% |
| 60S ribosomal protein L3 OS = Homo sapiens OX = 9606 GN = RPL3 PE = 1 SV = 2 | P39023 | RPL3 | 46 kDa | 5 | 4 | 1 | 1 | 100% | 8% |
| Heterogeneous nuclear ribonucleoprotein H OS = Homo sapiens OX = 9606 GN = HNRNPH1 PE = 1 SV = 4 | P31943 | HNRNPH1 | 49 kDa | 3 | 3 | 1 | 1 | 100% | 98% |
| Desmoglein-1 OS = Homo sapiens OX = 9606 GN = DSG1 PE = 1 SV = 2 | Q02413 | DSG1 | 114 kDa | 2 | 2 | 1 | 1 | 100% | 97% |
| 40S ribosomal protein S2 OS = | P15880 | RPS2 | 31 kDa | 2 | 2 | 1 | 1 | 100% | 96% |
| Identified proteins (276) | Accession number | Alternate ID | Molecular weight | Quantitative value (total spectra) PERK-BirA | Exclusive unique peptide count PERK-BirA | Quantitative value (total spectra) Control | Exclusive unique peptide count Control | Protein identification probability PERK-BirA | Protein identification probability Control |
|--------------------------|------------------|--------------|------------------|---------------------------------------------|-----------------------------------------|-------------------------------------------|------------------------------------------|---------------------------------------------|---------------------------------------------|
| Homo sapiens OX = 9606 GN = RPS2 PE = 1 SV = 2 | P81605 | DCD | 11 kDa | 2 | 2 | 1 | 1 | 100% | 94% |
| Dermcidin OS = Homo sapiens OX = 9606 GN = DCD PE = 1 SV = 2 | | | | | | | | | |
| 40S ribosomal protein S16 OS = Homo sapiens OX = 9606 GN = RPS16 PE = 1 SV = 2 | P62249 | RPS16 | 16 kDa | 2 | 2 | 1 | 1 | 100% | 92% |
| Heterogeneous nuclear ribonucleoprotein M OS = Homo sapiens OX = 9606 GN = HNRNPM PE = 1 SV = 3 | P52272 | HNRNPM | 78 kDa | 2 | 2 | 1 | 1 | 100% | 92% |
| Serine/arginine-rich splicing factor 7 OS = Homo sapiens OX = 9606 GN = SRSF7 PE = 1 SV = 1 | Q16629 | SRSF7 | 27 kDa | 3 | 3 | 1 | 1 | 99% | 77% |
| 40S ribosomal protein S15a OS = Homo sapiens OX = 9606 GN = RPS15A PE = 1 SV = 2 | P62244 | RPS15A | 15 kDa | 3 | 3 | 1 | 1 | 100% | 74% |
| T-complex protein 1 subunit alpha OS = Homo sapiens OX = 9606 GN = TCP1 PE = 1 SV = 1 | P17987 | TCP1 | 60 kDa | 3 | 3 | 1 | 1 | 100% | 56% |
| Pre-mRNA-processing factor 40 homolog A OS = Homo sapiens OX = 9606 GN = PRPF40A PE = 1 SV = 2 | O75400 | PRPF40A | 109 kDa | 3 | 3 | 1 | 1 | 99% | 50% |
| Glyceraldehyde-3-phosphate dehydrogenase OS = Homo sapiens OX = 9606 GN = GAPDH PE = 1 SV = 3 | P04406 | GAPDH | 36 kDa | 2 | 2 | 1 | 1 | 100% | 31% |
| RNA-binding protein 39 OS = Homo sapiens OX = 9606 GN = RBM39 PE = 1 SV = 2 | Q14498 | RBM39 | 59 kDa | 3 | 3 | 1 | 1 | 99% | 28% |
| Probable ATP-dependent RNA helicase DDX46 OS = Homo | Q7L014 | DDX46 | 117 kDa | 3 | 3 | 1 | 1 | 100% | 8% |

(continued)
| Identified proteins (276) | Accession number | Alternate ID | Molecular weight | Quantitative value (total spectra) | Exclusive unique peptide count PERK-BirA | Quantitative value (total spectra) Control | Exclusive unique peptide count Control | Protein identification probability PERK-BirA | Protein identification probability Control |
|--------------------------|------------------|--------------|------------------|-----------------------------------|------------------------------------------|------------------------------------------|------------------------------------------|--------------------------------------------|--------------------------------------------|
| sapiens OX = 9606 GN = DDX46 PE = 1 SV = 2 | Q5D862 | FLG2 | 248 kDa | 3 | 3 | 1 | 1 | 85% | 23% |
| Filaggrin-2 OS = Homo sapiens OX = 9606 GN = FLG2 PE = 1 SV = 1 | | | | | | | | | |
| Cofilin-1 OS = Homo sapiens OX = 9606 GN = CFL1 PE = 1 SV = 3 | P23528 | CFL1 | 19 kDa | 3 | 3 | 1 | 1 | 100% | 7% |
| Heterogeneous nuclear ribonucleoprotein A/B OS = Homo sapiens OX = 9606 GN = HNRNPAB PE = 1 SV = 2 | Q99729 | HNRNPAB | 36 kDa | 2 | 2 | 1 | 1 | 98% | 98% |
| Pre-mRNA-processing-splicing factor 8 OS = Homo sapiens OX = 9606 GN = PRPF8 PE = 1 SV = 2 | Q6P2Q9 | PRPF8 | 274 kDa | 4 | 4 | 1 | 1 | 85% | 31% |
| Elongation factor Tu, mitochondrial OS = Homo sapiens OX = 9606 GN = TUFM PE = 1 SV = 2 | P49411 | TUFM | 50 kDa | 9 | 8 | 2 | 2 | 100% | 95% |
| RNA-binding protein FUS OS = Homo sapiens OX = 9606 GN = FUS PE = 1 SV = 1 | P35637 | FUS | 53 kDa | 11 | 6 | 2 | 2 | 100% | 30% |
| Peroxiredoxin-2 OS = Homo sapiens OX = 9606 GN = PRDX2 PE = 1 SV = 5 | P32119 | PRDX2 | 22 kDa | 6 | 3 | 2 | 1 | 100% | 73% |
| ADP-ribosylation factor-like protein 6-interacting protein 4 OS = Homo sapiens OX = 9606 GN = ARL6IP4 PE = 1 SV = 2 | Q66P3J | ARL6IP4 | 45 kDa | 6 | 4 | 2 | 1 | 100% | 98% |
| Nucleolar RNA helicase 2 OS = Homo sapiens OX = 9606 GN = DDX21 PE = 1 SV = 5 | Q9NR30 | DDX21 | 87 kDa | 7 | 7 | 2 | 2 | 100% | 96% |
| Fibronectin OS = Homo sapiens OX = 9606 GN = FN1 PE = 1 SV = 4 | P02751 | FN1 | 263 kDa | 4 | 3 | 2 | 2 | 100% | 100% |

(continued)
| Identified proteins (276) | Accession number | Alternate ID | Molecular weight | Quantitative value (total spectra) | Exclusive peptide count PERK-BirA | Quantitative value (total spectra) Control | Exclusive peptide count Control | Protein identification probability PERK-BirA | Protein identification probability Control |
|--------------------------|------------------|--------------|------------------|-----------------------------------|----------------------------------|------------------------------------------|--------------------------------|------------------------------------------|-----------------------------------------------|
| Serine/arginine-rich splicing factor 1 OS = Homo sapiens OX = 9606 GN = SRSF1 PE = 1 SV = 2 | Q07955 | SRSF1 | 28 kDa | 5 | 4 | 2 | 2 | 100% | 66% |
| Serine/threonine-protein kinase PRP4 homolog OS = Homo sapiens OX = 9606 GN = PRPF4B PE = 1 SV = 3 | Q13523 | PRPF4B | 117 kDa | 4 | 4 | 2 | 2 | 100% | 100% |
| Nucleolar protein 58 OS = Homo sapiens OX = 9606 GN = NOP58 PE = 1 SV = 1 | Q9Y2X3 | NOP58 | 60 kDa | 4 | 4 | 2 | 2 | 100% | 100% |
| Alpha-enolase OS = Homo sapiens OX = 9606 GN = ENO1 PE = 1 SV = 2 | P06733 | ENO1 | 47 kDa | 4 | 3 | 2 | 2 | 100% | 98% |
| Histone H2A type 1 OS = Homo sapiens OX = 9606 GN = HIST1H2AG PE = 1 SV = 2 | P0C0S8 (+6) | HIST1H2AG | 14 kDa | 2 | 2 | 2 | 2 | 100% | 100% |
| Serine/arginine-rich splicing factor 2 OS = Homo sapiens OX = 9606 GN = SRSF2 PE = 1 SV = 4 | Q01130 | SRSF2 | 25 kDa | 2 | 2 | 2 | 2 | 100% | 100% |
| 60S ribosomal protein L36a OS = Homo sapiens OX = 9606 GN = RPL36A PE = 1 SV = 2 | P83881 (+1) | RPL36A | 12 kDa | 2 | 2 | 2 | 2 | 99% | 93% |
| Poly(rC)-binding protein 2 OS = Homo sapiens OX = 9606 GN = PCBP2 PE = 1 SV = 1 | Q15366 | PCBP2 | 39 kDa | 4 | 1 | 2 | 2 | 100% | 71% |
| Proliferation-associated protein 2G4 OS = Homo sapiens OX = 9606 GN = PA2G4 PE = 1 SV = 3 | Q9UQ80 | PA2G4 | 44 kDa | 4 | 4 | 2 | 2 | 100% | 71% |
| 40S ribosomal protein S26 OS = Homo sapiens OX = 9606 GN = RPS26 PE = 1 SV = 3 | P62854 | RPS26 | 13 kDa | 2 | 2 | 2 | 1 | 100% | 67% |
| Keratinocyte proline-rich protein OS = Homo sapiens OX = | Q5T749 | KPRP | 64 kDa | 2 | 2 | 2 | 2 | 73% | 85% |

(continued)
| Identified proteins (276) | Accession number | Alternate ID | Molecular weight | Quantitative value (total spectra) PERK-BirA | Exclusive unique peptide count PERK-BirA | Quantitative value (total spectra) Control | Exclusive unique peptide count Control | Protein identification probability PERK-BirA | Protein identification probability Control |
|-------------------------|------------------|--------------|------------------|---------------------------------------------|-----------------------------------------|-------------------------------------------|------------------------------------------|---------------------------------|---------------------------------|
| 9606 GN = KPRP PE = 1 SV = 1 | O00571 | DDX3X | 73 kDa | 2 | 2 | 2 | 2 | 100% | 27% |
| ATP-dependent RNA helicase DDX3X OS = Homo sapiens OX = 9606 GN = DDX3X PE = 1 SV = 3 | P53396 | ACLY | 121 kDa | 5 | 5 | 2 | 2 | 100% | 16% |
| ATP-citrate synthase OS = Homo sapiens OX = 9606 GN = ACLY PE = 1 SV = 3 | P36578 | RPL4 | 48 kDa | 3 | 3 | 2 | 2 | 100% | 15% |
| 60S ribosomal protein L4 OS = Homo sapiens OX = 9606 GN = RPL4 PE = 1 SV = 5 | P62424 | RPL7A | 30 kDa | 2 | 2 | 2 | 1 | 92% | 10% |
| 60S ribosomal protein L7a OS = Homo sapiens OX = 9606 GN = RPL7A PE = 1 SV = 2 | P62917 | RPL8 | 28 kDa | 1 | 1 | 2 | 2 | 83% | 98% |
| 60S ribosomal protein L8 OS = Homo sapiens OX = 9606 GN = RPL8 PE = 1 SV = 2 | Q6ZUT1 | NKAPD1 | 34 kDa | 2 | 2 | 2 | 2 | 60% | 66% |
| Uncharacterized protein NKAPD1 OS = Homo sapiens OX = 9606 GN = NKAPD1 PE = 1 SV = 2 | P09211 | GSTP1 | 23 kDa | 1 | 1 | 2 | 2 | 71% | 46% |
| Glutathione S-transferase P OS = Homo sapiens OX = 9606 GN = GSTP1 PE = 1 SV = 2 | Q12906 | ILF3 | 95 kDa | 0 | 0 | 2 | 2 | 0 | 100% |
| Interleukin enhancer-binding factor 3 OS = Homo sapiens OX = 9606 GN = ILF3 PE = 1 SV = 3 | P05114 | HMGN1 | 11 kDa | 1 | 1 | 2 | 2 | 9% | 31% |
| Non-histone chromosomal protein HMG-14 OS = Homo sapiens OX = 9606 GN = HMGN1 PE = 1 SV = 3 | Q08211 | DHX9 | 141 kDa | 20 | 15 | 3 | 2 | 100% | 98% |

(continued)
| Identified proteins (276) | Accession number | Alternate ID | Molecular weight | Quantitative value (total spectra) | Exclusive unique peptide count | Quantitative value (total spectra) | Exclusive unique peptide count | Protein identification probability | Protein identification probability |
|--------------------------|------------------|--------------|------------------|----------------------------------|-------------------------------|----------------------------------|-------------------------------|--------------------------------|--------------------------------|
| Peroxiredoxin-1 OS = Homo sapiens OX = 9606 GN = PRDX1 PE = 1 SV = 1 | Q06830 | PRDX1 | 22 kDa | 13 | 11 | 3 | 3 | 100% | 100% |
| Retinitis pigmentosa 9 protein OS = Homo sapiens OX = 9606 GN = RP9 PE = 1 SV = 2 | Q8TA86 | RP9 | 26 kDa | 11 | 8 | 3 | 3 | 100% | 100% |
| Non-POU domain-containing octamer-binding protein OS = Homo sapiens OX = 9606 GN = NONO PE = 1 SV = 4 | Q15233 | NONO | 54 kDa | 12 | 9 | 3 | 2 | 100% | 100% |
| L-lactate dehydrogenase B chain OS = Homo sapiens OX = 9606 GN = LDHB PE = 1 SV = 2 | P07195 | LDHB | 37 kDa | 7 | 5 | 3 | 2 | 100% | 100% |
| Vimentin OS = Homo sapiens OX = 9606 GN = VIM PE = 1 SV = 4 | P08670 | VIM | 54 kDa | 7 | 6 | 3 | 2 | 100% | 100% |
| 40S ribosomal protein S3a OS = Homo sapiens OX = 9606 GN = RPS3A PE = 1 SV = 2 | P61247 | RPS3A | 30 kDa | 3 | 3 | 3 | 3 | 100% | 100% |
| THO complex subunit 4 OS = Homo sapiens OX = 9606 GN = ALYREF PE = 1 SV = 3 | Q86V81 | ALYREF | 27 kDa | 2 | 2 | 3 | 2 | 100% | 100% |
| Histone H1x OS = Homo sapiens OX = 9606 GN = H1FX PE = 1 SV = 1 | Q92522 | H1FX | 22 kDa | 3 | 2 | 3 | 2 | 100% | 100% |
| 40S ribosomal protein S14 OS = Homo sapiens OX = 9606 GN = RPS14 PE = 1 SV = 3 | P62263 | RPS14 | 16 kDa | 2 | 2 | 3 | 2 | 100% | 97% |
| 60S ribosomal protein L13 OS = Homo sapiens OX = 9606 GN = RPL13 PE = 1 SV = 4 | P26373 | RPL13 | 24 kDa | 2 | 2 | 3 | 2 | 100% | 100% |
| Serum albumin OS = Homo sapiens OX = 9606 GN = ALB PE = 1 SV = 2 | P02768 | ALB | 69 kDa | 2 | 1 | 3 | 3 | 96% | 100% |
| Elongation factor 1-gamma OS = | P26641 | EEF1G | 50 kDa | 1 | 1 | 3 | 3 | 97% | 100% |

(continued)
Table 1.  Continued.

| Identified proteins (276) | Accession number | Alternate ID | Molecular weight | Quantitative value (total spectra) PERK-BirA | Exclusive unique peptide count PERK-BirA | Quantitative value (total spectra) Control | Exclusive unique peptide count Control | Protein identification probability PERK-BirA | Protein identification probability Control |
|--------------------------|------------------|--------------|------------------|---------------------------------------------|----------------------------------------|------------------------------------------|----------------------------------------|--------------------------------------------|---------------------------------------------|
| Homo sapiens OX = 9606 GN = EEF1G PE = 1 SV = 3 | P62906 | RPL10A | 25 kDa | 1 | 1 | 3 | 2 | 41% | 98% |
| 60S ribosomal protein L10a OS = Homo sapiens OX = 9606 GN = RPL10A PE = 1 SV = 2 | P25705 | ATP5F1A | 60 kDa | 1 | 1 | 3 | 3 | 8% | 100% |
| ATP synthase subunit alpha, mitochondrial OS = Homo sapiens OX = 9606 GN = ATP5F1A PE = 1 SV = 1 | | | | | | | | | |
| Heat shock protein HSP 90-alpha OS = Homo sapiens OX = 9606 GN = HSP90AA1 PE = 1 SV = 5 | P07900 | HSP90AA1 | 85 kDa | 12 | 9 | 4 | 3 | 100% | 100% |
| Pyruvate kinase PKM OS = Homo sapiens OX = 9606 GN = PKM PE = 1 SV = 4 | P14618 | PKM | 58 kDa | 15 | 15 | 4 | 4 | 100% | 100% |
| Heat shock protein HSP 90-beta OS = Homo sapiens OX = 9606 GN = HSP90AB1 PE = 1 SV = 4 | P08238 | HSP90AB1 | 83 kDa | 10 | 4 | 4 | 1 | 100% | 8% |
| Splicing factor, arginine/serine-rich 19 OS = Homo sapiens OX = 9606 GN = SCAF1 PE = 1 SV = 3 | Q9H7N4 | SCAF1 | 139 kDa | 8 | 7 | 4 | 3 | 100% | 100% |
| Heterogeneous nuclear ribonucleoprotein K OS = Homo sapiens OX = 9606 GN = HNRNPK PE = 1 SV = 1 | P61978 | HNRNPK | 51 kDa | 5 | 5 | 4 | 4 | 100% | 100% |
| Trypsin-1 OS = Homo sapiens OX = 9606 GN = PRSS1 PE = 1 SV = 1 | P07477 | PRSS1 | 27 kDa | 4 | 2 | 4 | 2 | 100% | 100% |
| 40S ribosomal protein S30 OS = Homo sapiens OX = 9606 GN = FAU PE = 1 SV = 1 | P62861 | FAU | 7 kDa | 3 | 1 | 4 | 2 | 97% | 100% |
| DNA topoisomerase 1 OS = Homo sapiens OX = 9606 GN = TOP1 PE = 1 SV = 2 | P11387 | TOP1 | 91 kDa | 6 | 5 | 4 | 4 | 100% | 97% |

(continued)
| Identified proteins (276) | Accession number | Alternate ID | Molecular weight | Quantitative value (total spectra) PERK-BirA | Exclusive unique peptide count PERK-BirA | Quantitative value (total spectra) Control | Exclusive unique peptide count Control | Protein identification probability PERK-BirA | Protein identification probability Control |
|--------------------------|------------------|--------------|------------------|--------------------------------------------|---------------------------------|-------------------------------------------|---------------------------------|---------------------------------|---------------------------------|
| 60S ribosomal protein L7 OS = Homo sapiens OX = 9606 GN = RPL7 PE = 1 SV = 1 | P18124 | RPL7 | 29 kDa | 4 | 3 | 4 | 3 | 100% | 100% |
| 40S ribosomal protein S8 OS = Homo sapiens OX = 9606 GN = RPS8 PE = 1 SV = 2 | P62241 | RPS8 | 24 kDa | 3 | 3 | 4 | 2 | 100% | 100% |
| 60S ribosomal protein L5 OS = Homo sapiens OX = 9606 GN = RPL5 PE = 1 SV = 3 | P46777 | RPL5 | 34 kDa | 1 | 1 | 4 | 2 | 95% | 80% |
| Ribosomal RNA processing protein 1 homolog B OS = Homo sapiens OX = 9606 GN = RRP1B PE = 1 SV = 3 | Q14684 | RRP1B | 84 kDa | 0 | 0 | 4 | 4 | 0 | 100% |
| Elongation factor 2 OS = Homo sapiens OX = 9606 GN = EEF2 PE = 1 SV = 4 | P13639 | EEF2 | 95 kDa | 31 | 19 | 5 | 5 | 100% | 100% |
| Tubulin beta chain OS = Homo sapiens OX = 9606 GN = TUBB PE = 1 SV = 2 | P07437 | TUBB | 50 kDa | 16 | 11 | 5 | 4 | 100% | 100% |
| Tubulin alpha-1B chain OS = Homo sapiens OX = 9606 GN = TUBA1B PE = 1 SV = 1 | P68363 (+2) | TUBA1B | 50 kDa | 13 | 8 | 5 | 4 | 100% | 100% |
| L-lactate dehydrogenase A chain OS = Homo sapiens OX = 9606 GN = LDHA PE = 1 SV = 2 | P00338 | LDHA | 37 kDa | 7 | 6 | 5 | 5 | 100% | 100% |
| E3 ubiquitin-protein ligase RBBP6 OS = Homo sapiens OX = 9606 GN = RBBP6 PE = 1 SV = 1 | Q7Z6E9 | RBBP6 | 202 kDa | 11 | 10 | 5 | 5 | 100% | 100% |
| Protein LLP homolog OS = Homo sapiens OX = 9606 GN = LLPH PE = 1 SV = 1 | Q9BRT6 | LLPH | 15 kDa | 7 | 4 | 5 | 3 | 100% | 100% |
| Probable ATP-dependent RNA helicase DDX17 OS = Homo sapiens OX = 9606 GN = DDX17 PE = 1 SV = 2 | Q92841 | DDX17 | 80 kDa | 4 | 3 | 5 | 4 | 100% | 100% |

(continued)
Table 1. Continued.

| Identified proteins (276) | Accession number | Alternate ID | Molecular weight | Quantitative value (total spectra) PERK-BirA | Exclusive unique peptide count PERK-BirA | Quantitative value (total spectra) Control | Exclusive unique peptide count Control | Protein identification probability PERK-BirA | Protein identification probability Control |
|--------------------------|------------------|--------------|-----------------|---------------------------------------------|-----------------------------------------|-------------------------------------------|------------------------------------------|---------------------------------------------|---------------------------------------------|
| Protein SREK1IP1 OS = Homo sapiens OX = 9606 GN = SREK1IP1 PE = 1 SV = 1 | Q8N9Q2 | SREK1IP1 | 18 kDa | 4 | 3 | 5 | 3 | 100% | 100% |
| RNA-binding motif protein, X chromosome OS = Homo sapiens OX = 9606 GN = RBMX PE = 1 SV = 3 | P38159 | RBMX | 42 kDa | 8 | 6 | 5 | 4 | 100% | 97% |
| Putative RNA-binding protein Luc7-like 2 OS = Homo sapiens OX = 9606 GN = LUC7L2 PE = 1 SV = 2 | Q9Y383 | LUC7L2 | 47 kDa | 2 | 2 | 5 | 4 | 99% | 100% |
| 60S ribosomal protein L37 OS = Homo sapiens OX = 9606 GN = RPL37 PE = 1 SV = 2 | P61927 | RPL37 | 11 kDa | 0 | 0 | 5 | 2 | 0 | 100% |
| Heat shock 70 kDa protein 1A OS = Homo sapiens OX = 9606 GN = HSPA1A PE = 1 SV = 1 | P0DMV8 (+1) | HSPA1A | 70 kDa | 20 | 16 | 6 | 6 | 100% | 100% |
| Heat shock cognate 71 kDa protein OS = Homo sapiens OX = 9606 GN = HSPA8 PE = 1 SV = 1 | P11142 | HSPA8 | 71 kDa | 18 | 8 | 6 | 4 | 100% | 100% |
| Heterogeneous nuclear ribonucleoproteins A2/B1 OS = Homo sapiens OX = 9606 GN = HNRNPA2B1 PE = 1 SV = 2 | P22626 | HNRNPA2B1 | 37 kDa | 16 | 11 | 6 | 4 | 100% | 100% |
| Histone H4 OS = Homo sapiens OX = 9606 GN = HIST1H4A PE = 1 SV = 2 | P62805 | HIST1H4A | 11 kDa | 9 | 7 | 6 | 5 | 100% | 100% |
| AP-3 complex subunit delta-1 OS = Homo sapiens OX = 9606 GN = AP3D1 PE = 1 SV = 1 | O14617 | AP3D1 | 130 kDa | 9 | 7 | 6 | 4 | 100% | 100% |
| Nucleolin OS = Homo sapiens OX = 9606 GN = NCL PE = 1 SV = 3 | P19338 | NCL | 77 kDa | 8 | 8 | 6 | 6 | 100% | 100% |
| A-kinase anchor protein 17A OS | Q02040 | AKAP17A | 81 kDa | 11 | 8 | 6 | 6 | 100% | 100% |

(continued)
| Identified proteins (276) | Accession number | Alternate ID | Molecular weight | Quantitative value (total spectra) PERK-BirA | Exclusive unique peptide count | Quantitative value (total spectra) Control | Exclusive unique peptide count | Protein identification probability PERK-BirA | Protein identification probability Control |
|--------------------------|------------------|--------------|------------------|---------------------------------------------|-----------------------------|---------------------------------------------|-----------------------------|---------------------------------------------|---------------------------------------------|
| = Homo sapiens OX = 9606 GN = AKAP17A PE = 1 SV = 2 60S ribosomal protein L6 OS = Homo sapiens OX = 9606 GN = RPL6 PE = 1 SV = 3 | Q02878 | RPL6 | 33 kDa | 2 | 2 | 6 | 4 | 95% | 100% |
| Heterogeneous nuclear ribonucleoprotein A1 OS = Homo sapiens OX = 9606 GN = HNRNPA1 PE = 1 SV = 5 | P09651 | HNRNPA1 | 39 kDa | 16 | 11 | 7 | 4 | 100% | 100% |
| La-related protein 7 OS = Homo sapiens OX = 9606 GN = LARP7 PE = 1 SV = 1 | Q4G0J3 | LARP7 | 67 kDa | 6 | 6 | 7 | 6 | 100% | 100% |
| G patch domain-containing protein 4 OS = Homo sapiens OX = 9606 GN = GPATCH4 PE = 1 SV = 2 | Q5T310 | GPATCH4 | 50 kDa | 5 | 5 | 7 | 6 | 100% | 100% |
| NF-kappa-B-activating protein OS = Homo sapiens OX = 9606 GN = NKAP PE = 1 SV = 1 | Q8NSF7 | NKAP | 47 kDa | 8 | 6 | 8 | 5 | 100% | 100% |
| 60S ribosomal protein L23a OS = Homo sapiens OX = 9606 GN = RPL23A PE = 1 SV = 1 | P62750 | RPL23A | 18 kDa | 8 | 6 | 8 | 4 | 100% | 100% |
| Histone H2B type 1-K OS = Homo sapiens OX = 9606 GN = HIST1H2BK PE = 1 SV = 3 | O60814 (+8) | HIST1H2BK | 14 kDa | 7 | 5 | 8 | 4 | 100% | 100% |
| Histone H3.1 OS = Homo sapiens OX = 9606 GN = HIST1H3A PE = 1 SV = 2 | P68431 (+3) | HIST1H3A | 15 kDa | 6 | 4 | 8 | 4 | 100% | 100% |
| Transcription initiation factor TFIID subunit 3 OS = Homo sapiens OX = 9606 GN = TAF3 PE = 1 SV = 1 | Q5VWG9 | TAF3 | 104 kDa | 6 | 6 | 8 | 7 | 100% | 100% |
| Keratin, type I cytoskeletal 17 OS = Homo sapiens OX = 9606 GN = KRT17 PE = 1 SV = 2 | Q04695 | KRT17 | 48 kDa | 12 | 3 | 9 | 2 | 100% | 76% |

(continued)
| Identified proteins (276) | Accession number | Alternate ID | Molecular weight | Quantitative value (total spectra) PERK-BirA | Exclusive unique peptide count PERK-BirA | Quantitative value (total spectra) Control | Exclusive unique peptide count Control | Protein identification probability PERK-BirA | Protein identification probability Control |
|---------------------------|------------------|--------------|------------------|-----------------------------------------------|----------------------------------------|---------------------------------------------|------------------------------------------|---------------------------------------------|---------------------------------------------|
| Heterogeneous nuclear ribonucleoproteins C1/C2 OS = Homo sapiens OX = 9606 GN = HRNPC PE = 1 SV = 4 | P07910          | HNRNPC       | 34 kDa           | 9                                             | 6                                      | 9                                           | 4                                        | 100%                                       | 100%                                       |
| Hornerin OS = Homo sapiens OX = 9606 GN = HRNR PE = 1 SV = 2 | Q86YZ3          | HRNR         | 282 kDa          | 12                                            | 9                                      | 10                                          | 7                                        | 100%                                       | 100%                                       |
| Heterogeneous nuclear ribonucleoprotein U OS = Homo sapiens OX = 9606 GN = HRNPU PE = 1 SV = 6 | Q00839          | HNRNPU       | 91 kDa           | 17                                            | 12                                     | 11                                          | 6                                        | 100%                                       | 100%                                       |
| Serine/arginine-rich splicing factor 11 OS = Homo sapiens OX = 9606 GN = SRSF11 PE = 1 SV = 1 | Q05519          | SRSF11       | 54 kDa           | 11                                            | 8                                      | 11                                          | 6                                        | 100%                                       | 100%                                       |
| Serine/arginine repetitive matrix protein 2 OS = Homo sapiens OX = 9606 GN = SRRM2 PE = 1 SV = 2 | Q9UQ35          | SRRM2        | 300 kDa          | 15                                            | 7                                      | 11                                          | 6                                        | 100%                                       | 100%                                       |
| Poly [ADP-ribose] polymerase 1 OS = Homo sapiens OX = 9606 GN = PARP1 PE = 1 SV = 4 | P09874          | PARP1        | 113 kDa          | 29                                            | 22                                     | 12                                          | 12                                       | 100%                                       | 100%                                       |
| Elongation factor 1-alpha 1 OS = Homo sapiens OX = 9606 GN = EEF1A1 PE = 1 SV = 1 | P68104 (+1)     | EEF1A1       | 50 kDa           | 21                                            | 14                                     | 13                                          | 9                                        | 100%                                       | 100%                                       |
| Nucleolar protein 56 OS = Homo sapiens OX = 9606 GN = NOP56 PE = 1 SV = 4 | O00567          | NOP56        | 66 kDa           | 16                                            | 11                                     | 13                                          | 10                                       | 100%                                       | 100%                                       |
| U2 snRNP-associated SURP motif-containing protein OS = Homo sapiens OX = 9606 GN = U2SURP PE = 1 SV = 2 | O15042          | U2SURP       | 118 kDa          | 25                                            | 19                                     | 14                                          | 10                                       | 100%                                       | 100%                                       |
| Guanine nucleotide-binding protein-like 3 OS = Homo sapiens OX = 9606 GN = GNL3 PE = 1 SV = 2 | Q9BVP2          | GNL3         | 62 kDa           | 9                                             | 7                                      | 16                                          | 9                                        | 100%                                       | 100%                                       |

(continued)
| Identified proteins (276) | Accession number | Alternate ID | Molecular weight | Quantitative value (total spectra) PERK-BirA | Exclusive unique peptide count PERK-BirA | Quantitative value (total spectra) Control | Exclusive unique peptide count Control | Protein identification probability | Protein identification probability Control |
|--------------------------|------------------|--------------|------------------|---------------------------------------------|------------------------------------------|---------------------------------------------|------------------------------------------|---------------------------------|---------------------------------|
| Actin, cytoplasmic 1 OS = Homo sapiens DX = 9606 GN = ACTB PE = 1 SV = 1 | P60709 (+1) | ACTB | 42 kDa | 22 | 12 | 17 | 9 | 100% | 100% |
| Multiple myeloma tumor-associated protein 2 OS = Homo sapiens DX = 9606 GN = MMTAG2 PE = 1 SV = 1 | Q9BU76 | MMTAG2 | 29 kDa | 21 | 13 | 17 | 8 | 100% | 100% |
| Keratin, type II cytoskeletal 5 OS = Homo sapiens DX = 9606 GN = KRT5 PE = 1 SV = 3 | P13647 | KRT5 | 62 kDa | 27 | 15 | 20 | 11 | 100% | 100% |
| Histone H1.0 OS = Homo sapiens DX = 9606 GN = H1F0 PE = 1 SV = 3 | P07305 | H1F0 | 21 kDa | 16 | 9 | 20 | 9 | 100% | 100% |
| Nucleolar protein of 40 kDa OS = Homo sapiens DX = 9606 GN = ZCCHC17 PE = 1 SV = 1 | Q9NP64 | ZCCHC17 | 28 kDa | 19 | 9 | 20 | 10 | 100% | 100% |
| 60S ribosomal protein L29 OS = Homo sapiens DX = 9606 GN = RPL29 PE = 1 SV = 2 | P47914 | RPL29 | 18 kDa | 10 | 2 | 21 | 5 | 100% | 100% |
| Keratin, type I cytoskeletal 14 OS = Homo sapiens DX = 9606 GN = KRT14 PE = 1 SV = 4 | P02533 | KRT14 | 52 kDa | 32 | 16 | 22 | 7 | 100% | 100% |
| Protein SON OS = Homo sapiens DX = 9606 GN = SON PE = 1 SV = 4 | P18583 | SON | 264 kDa | 15 | 15 | 23 | 17 | 100% | 100% |
| Keratin, type II cytoskeletal 6A OS = Homo sapiens DX = 9606 GN = KRT6A PE = 1 SV = 3 | P02538 | KRT6A | 60 kDa | 30 | 8 | 25 | 7 | 100% | 100% |
| Transcription termination factor 1 OS = Homo sapiens DX = 9606 GN = TTF1 PE = 1 SV = 3 | Q15361 | TTF1 | 103 kDa | 31 | 23 | 25 | 17 | 100% | 100% |
| Treacle protein OS = Homo sapiens DX = 9606 GN = TCOF1 PE = 1 SV = 3 | Q13428 | TCOF1 | 152 kDa | 26 | 17 | 27 | 17 | 100% | 100% |
| Methylcrotonoyl-CoA | Q96RQ3 | MCCC1 | 80 kDa | 50 | 25 | 40 | 19 | 100% | 100% |

(continued)
| Identified proteins (276)                                                                 | Accession number | Alternate ID | Molecular weight | Quantitative value (total spectra) | Exclusive unique peptide count | Quantitative value (total spectra) | Exclusive unique peptide count | Protein identification probability PERK-BirA | Protein identification probability Control |
|-------------------------------------------------------------------------------------------------------------------------------------|------------------|--------------|------------------|-----------------------------------|--------------------------------|-----------------------------------|-----------------------------------|---------------------------------------------|---------------------------------------------|
| carboxylase subunit alpha, mitochondrial OS = Homo sapiens OX = 9606 GN = MCCC1 PE = 1 SV = 3                                                                                           | Q1ED39           | KNOP1        | 52 kDa           | 61                                | 33                             | 42                                | 23                                | 100%                                        | 100%                                        |
| Lysine-rich nucleolar protein 1 OS = Homo sapiens OX = 9606 GN = KNOP1 PE = 1 SV = 1                                                                                                          | Q9NWB6           | ARGLU1       | 33 kDa           | 29                                | 17                             | 46                                | 20                                | 100%                                        | 100%                                        |
| Arginine and glutamate-rich protein 1 OS = Homo sapiens OX = 9606 GN = ARGLU1 PE = 1 SV = 1                                                                                                  | Q9NX58           | LYAR         | 44 kDa           | 50                                | 24                             | 50                                | 23                                | 100%                                        | 100%                                        |
| Cell growth-regulating nucleolar protein OS = Homo sapiens OX = 9606 GN = LYAR PE = 1 SV = 2                                                                                                  |                 |              |                  |                                   |                                |                                   |                                   |                                             |                                             |
| Keratin, type I cytoskeletal 9 OS = Homo sapiens OX = 9606 GN = KRT9 PE = 1 SV = 3                                                                                                           | P35527           | KRT9         | 62 kDa           | 98                                | 34                             | 54                                | 19                                | 100%                                        | 100%                                        |
| Keratin, type I cytoskeletal 10 OS = Homo sapiens OX = 9606 GN = KRT10 PE = 1 SV = 6                                                                                                          | P13645           | KRT10        | 59 kDa           | 60                                | 27                             | 54                                | 24                                | 100%                                        | 100%                                        |
| Keratin, type II cytoskeletal 2 epidermal OS = Homo sapiens OX = 9606 GN = KRT2 PE = 1 SV = 2                                                                                                 | P35908           | KRT2         | 65 kDa           | 64                                | 29                             | 60                                | 24                                | 100%                                        | 100%                                        |
| Histone H1.2 OS = Homo sapiens OX = 9606 GN = HIST1H1C PE = 1 SV = 2                                                                                                                       | P16403           | HIST1H1C     | 21 kDa           | 72                                | 2                              | 69                                | 2                                 | 100%                                        | 100%                                        |
| Acetyl-CoA carboxylase 1 OS = Homo sapiens OX = 9606 GN = ACACA PE = 1 SV = 2                                                                                                               | Q13085           | ACACA        | 266 kDa          | 41                                | 33                             | 69                                | 45                                | 100%                                        | 100%                                        |
| Histone H1.4 OS = Homo sapiens OX = 9606 GN = HIST1H1E PE = 1 SV = 2                                                                                                                       | P10412           | HIST1H1E     | 22 kDa           | 74                                | 13                             | 75                                | 18                                | 100%                                        | 100%                                        |
| Keratin, type II cytoskeletal 1 OS                                                                                                                                                    | P04264           | KRT1         | 66 kDa           | 135                               | 45                             | 94                                | 31                                | 100%                                        | 100%                                        |

(continued)
more studied of the two at MCS, and because both proteins are highly similar, for simplicity, here we focused on VAPB. We tested the possible interaction between VAPB and PERK by co-immunoprecipitation (co-IP) experiments and successfully confirmed that immunoprecipitation of wild type PERK-myc (PERKWT) expressed in HEK293-T cells, pulled down VAPB (Figures 2 and S2). In previous studies, we showed that the function of PERK required at the ER-mitochondria and ER-PM contacts was independent of its kinase function (van Vliet et al., 2017; Verfaillie et al., 2012). Here, to investigate whether PERK’s kinase activity was dispensable for PERK-VAPB interaction, we performed the IP in cells expressing either a PERKWT or a kinase dead mutant of PERK (PERKKD). Interestingly, the expression of the PERKKD mutant yielded no difference in VAPB binding (Figures 2 and S2). Together these observations suggest that PERK interacts with VAPB constitutively, and in the absence of a signal, evoking its UPR activation. It is possible that VAPB could recruit PERK to specific MCS upon certain stresses, or vice versa; further research would be needed to validate this possibility.

Table 1. Continued.

| Identified proteins (276) | Accession number | Alternate ID | Molecular weight | Quantitative value (total spectra) PERK-BirA | Exclusive unique peptide count PERK-BirA | Quantitative value (total spectra) Control | Exclusive unique peptide count Control | Protein identification probability PERK-BirA | Protein identification probability Control |
|--------------------------|------------------|-------------|------------------|---------------------------------------------|-----------------------------------------|---------------------------------------------|------------------------------------------|-----------------------------------------|------------------------------------------|
| = Homo sapiens OX = 9606 GN = KRT1 PE = 1 SV = 6 Propionyl-CoA carboxylase alpha chain, mitochondrial OS = Homo sapiens OX = 9606 GN = PCCA PE = 1 SV = 4 | P05165 | PCCA | 80 kDa | 117 | 49 | 114 | 45 | 100% | 100% |
| = Homo sapiens OX = 9606 GN = PC PE = 1 SV = 2 Pyruvate carboxylase, mitochondrial OS = Homo sapiens OX = 9606 GN = PC PE = 1 SV = 2 | P11498 | PC | 130 kDa | 122 | 54 | 121 | 49 | 100% | 100% |
PERK Interaction With SERCA2

SERCA12, an ATPase located in the ER membrane that pumps Ca\(^{2+}\) ions from the cytosol into the ER lumen, contains an FFNT motif at location 283 of the protein, which is located in the lumen of the ER. This study, along with others, does give support for a functional role between PERK and VAPA/B and other MCS proteins.

In contrast to SERCA2, no unique peptides for SERCA1 were identified in the BioID data set, so the presence of SERCA1 luminal Ca\(^{2+}\) pump Ca\(^{2+}\) leak from various sources (translocon, mitochondrial 1,4,5-trisphosphate receptor) and maintaining a high level of Ca\(^{2+}\) in the ER lumen, contributing to the ER stress response.

For example, the initial study reporting BioID as a tool to screen protein-protein interactions, BiDD (or TuboID) used only positive controls to detect false positives (Murphy & Levine, 2016). Our previous results indicated that PERK interaction with SERCA2 is an intriguing interaction with FFAT motif (two phenylalanines (FF)) in an acidic tract) that binds the major sperm protein (MSP) on VAP (Murphy & Levine, 2016). However, using a previously published algorithm (Murphy & Levine, 2016), we identified no robust FFAT motif in PERK interactions with SERCA2.

Conclusions and Limitations of the Study

In this report, we show a BioID dataset obtained by tagging the endogenous biotinylated PERK with a biotin ligase has been mutated to biotinylated ligase (VAPome) as a negative control for PERK interaction with SERCA2. Previous results indicated that PERK interaction with SERCA2 may be located close to the site of STIM1/OMI4 contact, playing a role in the regulation of SOCE activation.

Recent studies using BioID (and derivatives of BioID like TuboID) not tagged to their protein of interest to control for non-specific binding events has been shown to play a role at ER-mitochondria contact sites (Chami et al., 2008). With VAPB, we have been able to detect PERK interaction with SERCA2, which was again detected independently of its kinase activity and strongly activated by increases in cytosolic Ca\(^{2+}\) levels (Figure 2 and S2). Our previous results indicated that PERK interaction with SERCA2 was detected using biotinylated PERK and SERCA2 by immunoblot. Input was loaded as an input versus 500 µg of total protein used for the immunoprecipitation (PERK IP) and interaction was detected using antibodies against PERK and SERCA2 after incubation with 10% of the total protein amount used for the immunoprecipitation (PERK IP). Data show are representative of N = 3 (VAPB; N = 2 independent experiments).
Biotinylation Assay, and Mass Spectrometry

Materials and Methods

Cell Lines and Transfection

BoiD, Biotinylation Assay, and Mass Spectrometry

BoiD was performed as described previously (Roux et al., 2018). A PERK-BioID was achieved by transiently transfecting HEK293-T cells using X-tremegene 9 (Roche, Germany). A PERK-BioID was performed as described previously (Roux et al., 2018). A PERK-BioID was achieved by transiently transfecting HEK293-T cells using X-tremegene 9 (Roche, Germany).

Immunoprecipitation

After 48 h of transfection with selected plasmids, cells were harvested, and proteins were extracted. The cell lysate was then subjected to immunoprecipitation using Protein A/G magnetic beads (Pierce) for 1.5 h at 4 °C. The beads were washed with 600 μl of wash buffer (1% CHAPS, 100 mM KCl, 150 mM NaCl, 1x protease inhibitor tablets, 10 μg/ml trypsin, 100 μg/ml PMSF, and 100 μg/ml aprotinin) and sonicated.

Immunoprecipitation

After 48 h of transfection with selected plasmids, cells were harvested, and proteins were extracted. The cell lysate was then subjected to immunoprecipitation using Protein A/G magnetic beads (Pierce) for 1.5 h at 4 °C. The beads were washed with 600 μl of wash buffer (1% CHAPS, 100 mM KCl, 150 mM NaCl, 1x protease inhibitor tablets, 10 μg/ml trypsin, 100 μg/ml PMSF, and 100 μg/ml aprotinin) and sonicated.

Immunoprecipitation

After 48 h of transfection with selected plasmids, cells were harvested, and proteins were extracted. The cell lysate was then subjected to immunoprecipitation using Protein A/G magnetic beads (Pierce) for 1.5 h at 4 °C. The beads were washed with 600 μl of wash buffer (1% CHAPS, 100 mM KCl, 150 mM NaCl, 1x protease inhibitor tablets, 10 μg/ml trypsin, 100 μg/ml PMSF, and 100 μg/ml aprotinin) and sonicated.

Immunoprecipitation

After 48 h of transfection with selected plasmids, cells were harvested, and proteins were extracted. The cell lysate was then subjected to immunoprecipitation using Protein A/G magnetic beads (Pierce) for 1.5 h at 4 °C. The beads were washed with 600 μl of wash buffer (1% CHAPS, 100 mM KCl, 150 mM NaCl, 1x protease inhibitor tablets, 10 μg/ml trypsin, 100 μg/ml PMSF, and 100 μg/ml aprotinin) and sonicated.
Ron, D., & Walter, P. (2007). Signal integration in the endoplasmic reticulum unfolded protein response. *Nature Reviews Molecular Cell Biology*, 8(7), 519–529. https://doi.org/10.1038/nrm2199

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