

**Supplementary Table 1.** The up and down regulation of protein in HBR-EV compared with HCT-EV from Volcano plot.

HBR-HCT	Protein	logFC	Annotation
Up	PFN1	0.79	PFN1 - profilin 1. Binds to actin and modifies the cytoskeleton's structure. Profilin inhibits actin polymerization at high concentrations while promoting it at low ones. It binds to PIP2 and prevents IP3 and DG from forming. Moreover, it prevents HTT and androgen receptor (AR) aggregation. G-actin binding is necessary for its inhibition of AR.
	B4DMI9	1.26	DLGAP5 - discs, large (Drosophila) homolog-associated protein 5. This protein shows a potential cell cycle regulator which may play a role in the carcinogenesis of cancer cells. The ubiquitin-proteasome pathway targets mitotic phosphoprotein. The possibility of a protein involved in adherent junction differentiation and integrity that could be relevant to epithelial cells' CDH1-mediated adhesion and signaling.
	LAMB2	1.98	LAMB2 - laminin, beta 2 (laminin S). It has been suggested that laminin interacts with other extracellular matrix components to mediate cell attachment, migration, and organization into tissues during embryonic development. It uses a high affinity receptor to bind to cells.
	B3KME6	2.19	CEP170 - centrosomal protein 170 kDa; It participates in the organization of microtubules.
	B3KNL3	2.21	TRPC6 - transient receptor potential cation channel, subfamily C, member 6; is suspected to form a non-selective calcium permeant cation channel that is activated by receptors. It possibly operates on a phosphatidylinositol second messenger system that is triggered by G-protein-coupled receptors or receptor tyrosine kinases. Independent of protein kinase C, activated by diacylglycerol in a membrane-delimiting manner.
	Q53FZ9	2.35	FASTK - Fas-activated serine/threonine kinase. It phosphorylates the splicing regulator TIA1, which encourages FAS exon 6 inclusion and the production of mRNA that codes for the receptor's pro-apoptotic form.
	Q9HB62	2.39	GLS2 - glutaminase 2 (liver, mitochondrial). It shows an important effect on the control of glutamine catabolism. It increases the synthesis of ATP in cells and supports mitochondrial respiration by catalyzing the synthesis of glutamate and alpha-ketoglutarate. It enhances the

		generation of glutathione and NADH, which boosts cellular antioxidant function. It possibly aid in stopping the growth of tumors.
H3BRI8	2.48	NUP93 - nucleoporin 93 kDa. It participates in the construction and/or maintenance of the nuclear pore complex (NPC). Nucleoporins may be anchored to the NPC but not to NUP153 or TPR.
Q5VVC8	2.63	RPL11 - ribosomal protein L11. It binds to 5S ribosomal RNA (by similarity). It is necessary for the development of the 60S ribosomal subunits and rRNA maturation. Encourages PML nucleolar location.
H0YGA8	2.72	GTPBP1 - GTP binding protein 1. It stimulates the target mRNA species to degrade. It contributes to the control of circadian mRNA stability. Possesses GTPase activity and GTP binding.
Q86VZ3	3.16	JPH2 - junctophilin 2. In excitable cells, junctional membrane complexes—which connect the plasma membrane to the endoplasmic or sarcoplasmic reticulum—are partly formed by Junctophilins. They give the cell surface and intracellular calcium release channels a structural basis for functional cross-talk. It is essential for appropriate intracellular Ca(2+) signaling in cardiac myocytes because JPH2 is involved in ryanodine receptor-mediated calcium ion release.
B2RAN2	3.57	VNN1 - vanin 1. Amidohydrolase that selectively breaks down one of the carboamide bonds in D-pantetheine, recycling vitamin B5 (pantothenic acid) and liberating cysteamine.
Q53G91	3.64	SLC16A3 - solute carrier family 16, member 3 (monocarboxylic acid transporter 4). This monocarboxylate transporter is proton-linked and facilitates the rapid passage of numerous monocarboxylates across the plasma membrane, including lactate, pyruvate, branched-chain oxo acids derived from leucine, valine, and isoleucine, and the ketone bodies acetoacetate, beta-hydroxybutyrate, and acetate.
O43708	4.47	GSTZ1 - glutathione S-transferase zeta 1. This bifunctional enzyme exhibits minimal glutathione-conjugating activity and maleylacetoacetate isomerase, ethacrynic acid, and 7-chloro-4-nitrobenz-2-oxa-1,3-diazole activity. It can also catalyze the glutathione-dependent oxygenation of dichloroacetic acid to glyoxylic acid in the degradation of amino acids. However, its glutathione peroxidase activity is low when working with T-butyl and cumene hydroperoxides.

	Q5VW36	4.66	FOCAD – focadhesin. It is a potential inhibitor of tumor growth in gliomas.
Down	G8XUU7	-5.5	GRM5 - glutamate receptor, metabotropic 5. Receptor for glutamate. The action from this receptor is mediated by a G-protein, which causes a calcium-activated chloride current and activates the phosphatidylinositol-calcium second messenger system.
	E7ET48	-5.14	Absent in melanoma 1-like.
	B4DK06	-4.97	DNM1 - dynamin 1. Microtubule-associated force-producing protein that can bind and hydrolyze GTP and is involved in the formation of microtubule bundles. Possibly, they are taking part in the trafficking of vesicles. Contributes to endocytosis mediated by receptors.
	A8K237	-4.14	CYB5R2 - cytochrome b5 reductase 2. NADH-cytochrome B-5 reductases have roles in drug metabolism, cholesterol biosynthesis, erythrocyte and methemoglobin reduction, and the desaturation and elongation of fatty acids (by similarity). It is accountable for spermatozoa's NADH-dependent lucigenin chemiluminescence by lowering lucigenin and 2-[4-iodophenyl]-3-[4-nitrophenyl]-5-[Disulfophenyl-2,4] Monosodium salt of tetrazolium-2H (WST-1).
	Q5VZM0	-3.2	RRAGB - Ras-related GTP binding B. This is a protein that binds nucleotides and forms heterodimeric Rag complexes. It is necessary for mTORC1's amino acid-induced relocalization to lysosomes and the GTPase RHEB's subsequent activation of these lysosomes. This is an important step in the process of amino acids activating the TOR signaling cascade. It participates in the RCC1/Ran-GTPase pathway as well.
	Q96M20	-2.73	CNBD2 - cyclic nucleotide binding domain containing 2.
	Q69YG3	-2.71	DEPDC1 - DEP domain containing 1. This domain potentially functions as a transcriptional corepressor in the regulation of transcription. By suppressing the transcription of the A20 gene, which results in the transport of NF-KB protein into the nucleus and the subsequent suppression of apoptosis in bladder cancer cells, the DEPDC1A-ZNF224 complex may be a key player in the development of bladder cancer.
	B4DS20	-2.7	MPP3 - membrane protein, palmitoylated 3 (MAGUK p55 subfamily member 3).

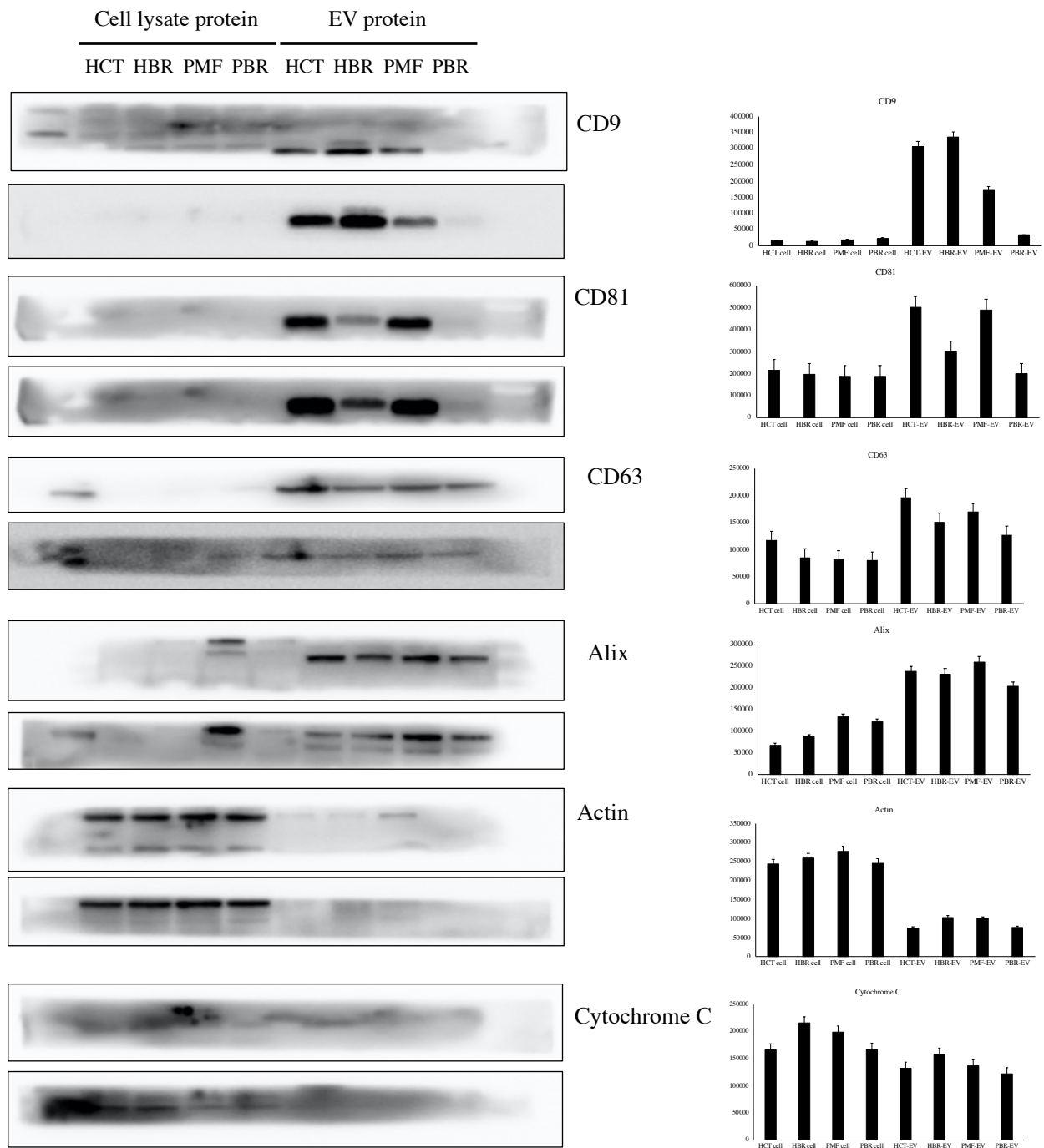
B4E2P8	-2.61	KDM3B - lysine (K)-specific demethylase 3B. Histone demethylase is essential to the function of histone code because it selectively demethylates histone H3's "Lys-9." Formaldehyde and succinate are produced when the Lys residue is demethylated. It can possibly acting as a tumor suppressor.
Q96D88	-2.54	PRR14 - proline rich 14.
Q59H97	-2.39	ZBTB11 - zinc finger and BTB domain containing 11. Potentially involved in transcriptional regulator.
G3V277	-2.38	WARS - tryptophanyl-tRNA synthetase. While T2-TrpRS lacks aminoacylation activity, isoforms 1, 2, and T1-TrpRS exhibit it. Whereas isoform 1 lacks angiostatic activity, isoforms 2, T1-TrpRS, and T2-TrpRS do. T2-TrpRS prevents endothelial cells from responding to fluid shear stress. Additionally, it controls the activation pathways of ERK, Akt, and eNOS that are linked to angiogenesis, cytoskeletal reorganization, and the expression of genes responsive to shear stress.
E9PP73	-2.38	COPB1 - coatamer protein complex, subunit beta 1. The cytosolic protein complex known as the coatamer binds to dilysine motifs, forming a reversible association with non-clathrin-coated Golgi vesicles. These vesicles aid in transporting biosynthetic proteins from the ER to the Golgi and trans Golgi network. Coatamer complex is necessary for dilysine-tagged protein transport from the Golgi to the ER in a retrograde manner and for budding from Golgi membranes.
C9J9N1	-2.11	GPR143 - G protein-coupled receptor 143. Receptor for dopamine, tyrosine, and L-DOPA. Following its binding to L-DOPA, it relocalizes beta arrestin at the plasma membrane, increases secretion of the neurotrophic factor SERPINF1, and stimulates Ca(2+) influx into the cytoplasm. In melanocytic cells. This ligand-dependent signaling occurs via a G(q)-mediated pathway in melanocytic cells. G proteins, which initiate the phosphoinositide signaling pathway, mediate its action.
LOEQU5	-2.07	TP53 - tumor protein p53. Depending on the cell type and physiological conditions, functions as a tumor suppressor in various tumor forms can cause either apoptosis or growth arrest. It is involved in regulating the cell cycle as a trans-activator that, through regulating several crucial genes, adversely controls the division of cells. A cyclin-dependent kinase inhibitor is one of the activated genes. The induction of apoptosis appears to be mediated by either upregulating the expression of FAS and BAX antigens or downregulating the expression of Bcl-2.

**Supplementary Table 2.** The up and down regulation of protein in PBR-EV compared with PMF-EV from Volcano plot.

<b>PBR-PMF</b>	<b>Protein</b>		<b>Annotation</b>
Up	NPEPPS	1.51	NPEPPS - aminopeptidase puromycin sensitive. Broad substrate specificity for multiple peptides in an aminopeptidase. Participates in proteolytic processes vital to the growth and survival of cells. Possibly serve as a neuropeptide activity regulator. It has a part in the mhc class i molecules' antigen-processing pathway. Engaged in the cytotoxic t-cell epitope precursors' n-terminal trimming. It also breaks down the poly-q peptides present in a variety of cellular proteins. It effectively digests tau from the normal brain than tau from the brain of an alzheimer's patient.
	O15354	1.55	GPR37 - G protein-coupled receptor 37 (endothelin receptor type B-like). The orphan receptor in the central nervous system may have a special functional role.
	Q8IVQ6	1.62	ZDHHC21 - zinc finger, DHHC-type containing 21. Sex steroid hormone receptors, such as ESR1, PGR, and AR, are palmitoylated, which controls how they target the plasma membrane. This impacts cAMP production and the fast intracellular signaling of sex hormones through ERK and AKT kinases. However, it does not effect the processes mediated by their nuclear receptor.
	E9PFI5	2.02	RPS3A - ribosomal protein S3A. It can potentially contribute to erythropoiesis by controlling the transcription factor DDIT3.
	Q5VSN0	2.07	SH3KBP1 - SH3-domain kinase binding protein 1. Adapter protein that controls a variety of signal transduction channels. Interacts with CBL and endophilins to regulate endocytosis and lysosomal degradation of ligand-induced receptor tyrosine kinases, such as EGFR and MET/hepatocyte growth factor receptor. An interaction with PDCD6IP and SPRY2 may inhibit the association with CBL and, consequently, the receptor internalization.
	Q9P225	2.12	DNAH2 - dynein, axonemal, heavy chain 2. The respiratory cilia's force-generating protein generates force towards the microtubule minus ends. Shows signs of ATPase activity. It is presumed that the release of ADP causes the force-producing power stroke. It is engaged in flagellar assembly and sperm motility.
	H0YLT7	2.18	PRTG – protogenin. This could contribute to the elongation of the anteroposterior axis.
	F8WD59	2.26	RPSA - ribosomal protein SA. Necessary for the 40S ribosomal subunit's stability and assembly. Necessary for the maturation of 18S rRNA in a subsequent stage of the maturation process of 40S ribosomal subunits through processing of the 20S rRNA-precursor. Serves as a laminin receptor on the cell surface and is involved in cell adhesion to the basement membrane, activating signaling transduction pathways. Possibly, it is involved in tissue morphogenesis and the determination of cell fate. Additionally, it serves as a receptor for several other ligands, such as bacteria, viruses, and the pathogenic prion protein.
	O75132	2.48	ZBED4 - zinc finger, BED-type containing 4.
	Q59HA1	2.54	GOLGA1 - golgin A1. Probably involved in preserving the Golgi apparatus.

	K9JA46	2.57	HSP90AA1 - heat shock protein 90 kDa alpha (cytosolic), class A member 1. Molecular chaperone which assists in the proper regulation, maturation, and structural maintenance of particular target proteins involved in signal transduction and cell cycle control. It exhibits a functional cycle that is connected to the activity of its atpase. This cycle likely causes the client proteins to undergo conformational changes, which activates them. Dynamically interacts with different co-chaperones to modify its atpase cycle, chaperone function, and substrate recognition.
	Q53EL8	2.73	NAP1L3 - nucleosome assembly protein 1-like 3.
	Q8N539	3.11	FIBCD1 - fibrinogen C domain containing 1. Acetyl group-binding receptor that binds to acetylated structures—like chitin, some N-acetylated carbohydrates, and amino acids—with high affinity and in a calcium-dependent manner, however, not to their non-acetylated counterparts. It can make acetylated component endocytosis easier.
	H0Y515	3.62	ZNF687 - zinc finger protein 687. Potentially a transcriptional regulator.
	B4DL56	3.89	GALNT6 - UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase 6 (GalNAc-T6). It transfers an N-acetyl-D-galactosamine residue to a serine or threonine residue on the protein receptor, which is the first reaction in the biosynthesis of O-linked oligosaccharides. This reaction is catalyzed. This could possibly involved in the production of oncofetal fibronectin. It possesses activity against fibronectin peptides, EA2, Muc1a, and Muc2.
Down	B4DI83	-5.77	LMAN2L - lectin, mannose-binding 2-like. This protein could impact the control of a subset of glycoproteins' export from the endoplasmic reticulum. It could act as an ERGIC-53 regulator.
	Q9HBP3	-4.29	ANGPT2 - angiopoietin 2. Participates with ANGPT1 for the binding site by binding to TEK/TIE2, thereby modifying ANGPT1 signaling. In the absence of ANGPT1, it can cause TEK/TIE2 to undergo tyrosine phosphorylation. Endothelial cell apoptosis may be induced by ANGPT2-mediated loosening of cell-matrix contacts without angiogenic inducers like VEGF, leading to vascular regression. Combined with VEGF, it could promote the migration and proliferation of endothelial cells, acting as a permissive angiogenic signal..
	Q59EA4	-4.21	PLD1 - phospholipase D1, phosphatidylcholine-specific. It is crucial stage in many cellular processes, such as the regulation of mitosis, membrane trafficking, and signal transduction. It may potentially plays a role in controlling the flow of perinuclear intravesicular membranes.
	H3BRI8	-3.67	NUP93 - nucleoporin 93 kDa. Participates in the assembly and maintenance of npcs. Nucleoporins may be anchored to the NPC yet not to NUP153 or TPR.
	F8VPE9	-3.07	SOAT2 - sterol O-acyltransferase 2. Contributes to the assembly of lipoproteins and the absorption of dietary cholesterol. It may function as a ligase and supply cholesteryl esters for lipoprotein secretion from hepatocytes and intestinal mucosa in addition to its acyltransferase activity.
	Q59ES2	-3.03	ITPR3 - inositol 1,4,5-trisphosphate receptor, type 3. It is a receptor for the second messenger that mediates the release of intracellular calcium, inositol 1,4,5-trisphosphate.
	E7ET48	-3.02	AIM1L - absent in melanoma 1-like.

F8WDN2	-2.98	TXN2 - thioredoxin 2. It exhibits an anti-apoptotic effect and is essential for controlling the potential of the mitochondrial membrane. It may contribute to the development of anti-tumor agent resistance. It can reduce dithiols.
H7C3S5	-2.91	STRADB - STE20-related kinase adaptor beta. Pseudokinase binds to and activates STK11/LKB1 when it forms a complex with CAB39/MO25 (CAB39/MO25alpha or CAB39L/MO25beta). Assumes the closed conformation that is characteristic of active protein kinases and binds STK11/LKB1 as a pseudosubstrate, causing STK11/LKB1 to change conformation and become active.
B2R7W6	-2.89	ZNF140 - zinc finger protein 140. It may function as a repressor in the regulation of transcription.
K7EIX6	-2.79	GIT1 - G protein-coupled receptor kinase interacting ArfGAP 1. Gtpase-activating protein belonging to the family of ADP ribosylation factors. It could act as a scaffold to assemble molecules for the creation of signaling modules that regulate adhesion, cytoskeletal organization, and vesicle trafficking. Increases the size and rate of protrusion formation, possibly that this is due to PAK1 being targeted to adhesions and the leading edge of lamellipodia. Cytoplasmic complexes that contain inactive non-tyrosine-phosphorylated paxillin.
F8WEL6	-2.61	ZNF567 - zinc finger protein 567. Potentially a transcriptional regulator.
G3V277	-2.59	WARS - tryptophanyl-tRNA synthetase. While T2-TrpRS lack aminoacylation activity, isoforms 1, 2, and T1-TrpRS exhibit it. Whereas isoform 1 lacks angiostatic activity, isoforms 2, T1-TrpRS, and T2-TrpRS do. T2-TrpRS prevents endothelial cells from responding to fluid shear stress. Additionally, it controls the activation pathways of ERK, Akt, and eNOS that are linked to angiogenesis, cytoskeletal reorganization, and the expression of genes responsive to shear stress.
D3DQ69	-2.59	SERBP1 - SERPINE1 mRNA binding protein 1.
I3L3D5	-2.42	PFN1 - profilin 1. It binds to actin and modifies the cytoskeleton's structure. Profilin inhibits actin polymerization at high concentrations while promoting it at low levels. It binds to PIP2 and prevents IP3 and DG from forming. It also prevents the aggregation of HTT and AR. G-actin binding is necessary for its inhibition of AR.



**Supplementary Fig. 1. The raw data of Western blot exposure images.** The left panel showed the whole blot images of each protein, and the right panel show intensity graph of each protein.