Table S1. Changes in signal transduction mediators observed in RMS cell lines following curcumin treatment.

Protein (modification)	A204	RH30	RD	Responsible Kinase	Phosphatase	Result/Process
AMPKα1 (T183)	↓	↓		AMPKα1, CAMKK1, CAMKK2, LKB1, MLK1	PPP2Cα	**(Activation, intracellular localization)**-The catalytic subunit of the cellular energy sensing protein kinase AMP-activated protein kinase (AMPK). Inhibits energy consuming cellular processes (transcription, translation, ribosome biogenesis, etc.) under conditions of low ATP. Enhances glucose uptake and regulates insulin signaling and glycolysis. Enhances transcriptional activity of transcription factors involved in regulating energy metabolism. Directly inhibits the mTORC1 complex under low nutrient conditions. Promotes autophagy. Regulates cell polarity. Regulates lipid biosynthesis. Phosphorylates and stabilizes β-catenin. Phosphorylation at this site leads to activation and can occur through AMP/ATP-dependent means as well as -independent.
AMPKα2 (T172)		↑		ATM, CAMKK2, LKB1, PLK1, TAK1	PPP2Cα	**(Activation, intracellular localization, protein degradation)**- The catalytic subunit of the cellular energy sensing protein kinase AMP-activated protein kinase (AMPK). Inhibits energy consuming cellular processes (transcription, translation, ribosome biogenesis, etc.) under conditions of low ATP. Enhances glucose uptake and regulates insulin signaling and glycolysis. Enhances transcriptional activity of transcription factors involved in regulating energy metabolism. Directly inhibits the mTORC1 complex under low nutrient conditions. Promotes autophagy. Regulates cell polarity. Regulates lipid biosynthesis. Phosphorylates and stabilizes β-catenin. Phosphorylation at this site leads to activation and can occur through AMP/ATP-dependent means as well as -independent.
Akt (S473)	↓		↓	AXL, CDK1, DNAPK, IKKε, ILK, LRRK2, Mer, MAPKAPK2, mTOR, PDK1, PIK3R1, PIKFYVE, PRKD1, PKCα, PKCβ, TBK1	PHLPP, PHLPP2, PPP1Cα, PPP2Cα, PTEN	**(Activation, intracellular localization)**-Ser/Thr kinase involved in cell proliferation, survival, and metabolism. Regulates glucose uptake. Is activated by insulin and insulin-like growth factor (IGF). Activation and subsequent phosphorylation and inhibition of the downstream kinase GSK3 promotes the storage of glucose in the form of glycogen. AKT kinases are activated in response to wide range of growth factors, cytokines and stress leading to enhancement of mTOR-dependent signaling, activation of NF-κB-dependent gene transcription, and stimulation of CREB1-dependent transcription. Regulates Forkhead box protein transcription factors. Promotes β-catenin stabilization through the inhibition of GSK3B. Promotes the synthesis of anti-apoptotic proteins and results in the sequestering and degradation of pro-apoptotic proteins. Phosphorylation on this site is required for full activity.
β-Catenin	↓			N/A	N/A	Transcriptional regulator of the WNT pathway. Under conditions favoring GSK3B activation, β-catenin is phosphorylated, ubiquitinated and degraded. In the presence of WNT or the inhibition of GSK3B kinase activity, β-catenin is not degraded but accumulates in the nucleus where it serves as a coactivator for transcription. Regulates cell adhesion and anchorage-independent growth, promotes neurogenesis, regulates insulin internalization.
Chk-2 (T68)		↑	↑	ATM, ATR, Chk2, DNAPK, PLK1, TTK, ZAK	PPM1D, PPP1Cα, PPP2Cα	**(Activation, intracellular localization)**-Ser/Thr kinase required for cell cycle checkpoint arrest primarily at the G2/M transition point. Has a role in DNA repair and apoptotic cell death induced by DNA double-strand breaks. Phosphorylation at this site enhances homodimerization and subsequently full kinase activation.
CREB (S133; i.e., S119)			↓	AKT1, ATM, DYRK3, MAPKAPK2, MSK1/2, p90RSK, RSK2/3, SGK1	PTEN	**(Transcriptional activation)**-Transcription factor which binds to the cAMP response element present in many promoters of cellular and viral genes. Involved in diverse cellular processes.
ERK1/2 (T202/Y204, T185/Y187)			↑	ERK1, JAK2, MEK1, MEK2 (ERK1), RET,	DUSP1 (ERK2), DUSP4 (ERK1), DUSP6 (ERK1),	**(Activation, intracellular localization)**-Ser/Thr kinases central to the MAP kinase family. Have diverse roles in proliferation, transcription, translation, survival, cell cycle/cell division. Directly phosphorylates and regulates several transcription factors and translation regulatory proteins.

					PTP1B, PPP2Cα, PTPRJ	
FAK (Y397)	↑		↓	FAK, FGR, Met, Src	DUSP3, PTEN, PTP-PEST, SHP-2	**(Activation, intracellular localization, protein degradation)**-Non-receptor protein tyrosine kinase involved in the regulation of cell adhesion, cell spreading, cell migration, cell proliferation, cell cycle progression, actin cytoskeletal rearrangements and apoptosis. Required for normal embryonic development (angiogenesis, heart development, and nervous system development) and osteogenesis. Acts downstream of membrane receptors (cytokine, chemokine, growth factor, integrin, G-protein coupled, and immune) where it becomes tyrosine phosphorylated and associates in complex with Src tyrosine kinase family members. Additional tyrosine phosphorylation of PYK2 transforms it into a scaffolding protein capable of stimulating PI3K/AKT/mTOR, RAS/RAF/MEK/ERK and SAPK/JNK1 pathways as well as the translocation of MDM2 to the nucleus where it leads to p53 degradation. Phosphorylation or autophosphorylation at Y397 creates a docking site for SRC kinase family members that are then responsible for subsequent phosphorylation of Y576 and Y577 to induce full FAK activity.
Fyn (Y420)	↓			AXL, Fyn	STEP	**(Intermolecular association)**-Non-receptor protein tyrosine kinase. Has a role in regulating cell growth and survival, immune response, cell motility, remodeling of the cytoskeleton and integrin signaling. Following phosphorylation at the C-terminus associates with focal adhesion kinase FAK1 allowing for FAK1 phosphorylation and activation. Phosphorylates β- and Δ-catenins to regulate cellular adhesions. Promotes T-cell differentiation following binding of the T-cell receptor (TCR) through a mechanism involving focal adhesion kinase PYK2. Responsible for CD28 stimulation induced VAV1 activation. Activation of FYN is inhibited by phosphorylation at Y531 and activated by its dephosphorylation. Autophosphorylation of Y420 is required for full activation.
HSP27 (S78/S82)		↑	↓	AKT1, MAPKAPK2, MAPKAPK3, p70S6Kβ, PKACα, PKG1 iso 2, PRKD1,	Unknown	**(Activation, intracellular localization, protein degradation)**-Heat shock protein which functions as a molecular chaperone. Has a role in stress resistance by assisting proteins to maintain the correct folded state. Stress-induced phosphorylation at S78 and S82 impairs chaperone activity.
HSP60			↓	N/A	N/A	A chaperonin involved in mitochondrial protein import. Also serves for correct folding of mitochondrial matrix proteins following stress.
JNK (T183/Y185, T221/Y223)			↑	ASK1 (JNK1), MEKK6 (JNK1), MKK4, MKK7	PPP5C (JNK1)	**(Activation)**-Involved in cell proliferation, transformation, migration, differentiation, and death. Activated in response to proinflammatory cytokines or cellular stress. Through interaction and phosphorylation of AP-1 transcription factor components, leads to activation of AP-1-dependent transcription. Inhibits replication initiation (JNK1). Inhibits rRNA synthesis upon ribotoxic stress by inactivating RNA pol I (JNK2). Promotes stress induced cell apoptosis by phosphorylating p53 and YAP1. Necessary for Th1 polarization of T-helper cells. Promotes the degradation of β-catenin (JNK2). Can promote the activation of autophagic pathways (JNK1). JNK3 is specific to cells of the nervous system.
c-Jun (S63)			↑	CDK3, ERK1/2/7, JNK1/2, PBK, PLK3, VRK1	PPP2Cα, PPP5C	**(Acetylation, transcriptional activity induced, protein stabilized)**-Transcription factor that is a component of the AP-1 transcription factor family. Activation stimulates multiple genes regulating diverse cellular processes.
p27 (T198)	↓			AKT1, CAMK1A, Pim1	Unknown	**(Altered protein stability, altered intracellular localization)**-Regulates cell cycle progression. Inhibits cyclin A- and cyclin E-CDK2 complexes but promotes cyclin D-CDK4 complexes depending on its phosphorylation (not only at this site).

p53 (S392)	↑		↓	CDK7, CDK9, CK2α1, CK2β, ERK1, LKB1, NuaK1, PKR	Unknown	**(Transcriptional activation, intracellular localization, altered protein stability)**-Transcription factor involved in DNA repair, apoptosis, and cell cycle regulation. Regulates the circadian clock. Regulates early ribogenesis. Activated in response to stress. Phosphorylation of S392 has been linked to p53 protein stability and transcriptional activity.
p53 (S46)			↓	ATM, CDK5, DYRK3, HIPK2, p38α, PKCδ	Unknown	**(Transcriptional activation, intracellular localization, altered protein stability)**-Transcription factor involved in DNA repair, apoptosis, and cell cycle regulation. Regulates the circadian clock. Regulates early ribogenesis. Activated in response to stress.
p70 (T389)	↓			mTOR, NEK6, p70S6K, PDK1, PIK3Cα	PHLPP, PHLPP2, PPP1Cγ	**(Activation, intracellular localization)**-Ser/Thr kinase activated downstream of mTOR in response to growth promoting stimuli. Phosphorylates various downstream targets to regulate protein synthesis at the level of initiation and elongation. Has a feedback regulatory role on mTORC1/2 signaling. Has a role in promoting TNFα-induced insulin resistance.
p70 (T421/S424; i.e., T444/S447)	↓			CDK1, ERK2	Unknown	**(Activation)**-Ser/Thr kinase activated downstream of mTOR in response to growth promoting stimuli. Phosphorylates various downstream targets to regulate protein synthesis at the level of initiation and elongation. Has a feedback regulatory role on mTORC1/2 signaling. Has a role in promoting TNFα-induced insulin resistance.
PRAS40 (T246)	↓			AKT1, DYRK3	Unknown	**(Activity inhibited)**-A negative regulatory subunit of the mTORC1 complex. Negative regulatory activity is relieved by phosphorylation on T246.
RSK1/2/3 (S380/S386/S377)	↓			Cot	Unknown	**(Activation, protein degradation, ubiquitination)**-Ser/Thr kinases downstream of ERK1/ERK2 responsible for regulation of proliferation, survival, and differentiation by modifying mTOR-dependent signaling. Directly influences factors regulating transcription and translation in response to mitogenic- or stress-mediated stimulation. Inhibits GSK3β activity by phosphorylating Ser9 of GSK3B. Promotes assembly of the translational preinitiation complex. Enhances CAP-dependent translation through phosphorylation of EIF4B. May suppress mTOR activity by phosphorylating TSC2. Involved in cell cycle regulation. Regulates osteoblast differentiation. Sites S380 (RSK1), S386 (RSK2), and S377 (RSK3) are activation promoting autophosphorylation sites.
Src (Y419)		↑		AXL, EphB2, GSK3β, PDGFRα/β, PKACα, SRC	PTEN, PTPN13, PTPRJ	A proto-oncogenic non-receptor tyrosine kinase which has a role in numerous signaling events in the cell. Is a central component of the Src receptor signaling complex.
STAT2 (Y689)	↓	↑		Lck	Unknown	**(Intracellular localization)**-Signal transducer and activator of transcription. Mediates signaling by type I interferons (IFNs). Important for inducing the antiviral state. Also acts as a negative feedback regulator of IFNAR2. Acts as a regulator of mitochondrial fission. Phosphorylation of Y689 favors nuclear localization.
STAT3 (Y705)	↓	↓		ALK, AXL, Fer, FGFR1, Fyn, JAK2, Mer, NEK6, PKM, PKR iso2, Ret iso3, Src, Trkα	DUSP2, PTPN13, PTPN2, PTPRδ, PTPRT iso1	**(Activation, intracellular localization, methylation, protein degradation)**-Signal transducer and activator of transcription. Mediates cellular responses to diverse interleukin (ILs) and growth factor receptor stimulation. Helps recruit coactivators of transcription to target genes. Involved in the T-cell inflammatory response. Cytoplasmic STAT3 can inhibit activation of the integrated stress response kinase PKR. Regulates β-cell insulin secretion. Phosphorylation at Y705 induces nuclear localization and transcriptional activation.

STAT3 (S727)	↓			BUB1, CDK5, ERK1, ERK2, GSKα/β, IRAK1, JNK1, JNK2 iso 2, NEK6, p38α, PKCδ, PKCε, RSK2	DUSP2	**(Activity altered, intracellular localization)**-Signal transducer and activator of transcription. Mediates cellular responses to diverse interleukin (ILs) and growth factor receptor stimulation. Helps recruit coactivators of transcription to target genes. Involved in the T-cell inflammatory response. Cytoplasmic STAT3 can inhibit activation of the integrated stress response kinase PKR. Regulates β-cell insulin secretion. Phosphorylation at S727 is required for maximal transcriptional activation by enhancing DNA binding.
TOR (S2448)		↑		AKT1, p70S6K	Unknown	**(Activation; intracellular localization)**-The central catalytic subunit of the mTORC1 and mTORC2 kinase complex, which act as major regulators of cellular growth, survival and metabolism in response to nutrients, stress, energy and growth factor stimulation. Is a downstream target of the PI3K-AKT pathway. Promotes protein synthesis through the phosphorylation of the eukaryotic initiation factor (eIF)-4E binding protein (4EBP) and promoting the modification of ribosomal S6 protein. Stimulates ribosome biogenesis by enhancing RNA pol III activity. Regulates autophagy through the phosphorylation of ULK1 and DAP.
WNK1 (T60)	↓			AKT1, MSK1, SGK1	Unknown	**(Activation)**-Ser/Thr kinase, regulates Na^{++}/K^{++}-chloride coupled receptors. Has a role in cytoskeletal reorganization.
Yes (Y426)	↑	↑		AXL, EphA2	Unknown	**(Activation)**-Non-receptor tyrosine kinase (non-RTK) stimulated downstream of various RTKs. Involved in cell growth, survival, apoptosis, cell adhesion, cytoskeletal remodeling, and differentiation. Regulates G1 and G2/M phases of the cell cycle. Required for AKT-mediated cell migration. Phosphorylation at Y426 blocks inhibitory phosphorylation.

Information presented was obtained from the PhosphositePlus data base (http://www.phosphosite.org) and the UniProtKB/SwissProt database (http://www.uniprot.org). Arrows in each row indicate whether the expression or phosphorylation of each indicated protein or modification was either upregulated (↑), downregulate (↓) or unchanged (blank). Columns referring to “Kinase” and “Phosphatase” refer to those enzymes known or predicted to modify the respective residues at those sites.