**Table S1. Cell density- and mechano-sensitive nucleocytoplasmic shuttling molecules.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Protein Name  *Gene Name* | MW  Human | Function | Year\* | Ref. |
| Sterol regulatory element-binding protein 1  *SREBP1* | 1147 | Transcription factor that regulates expression of genes involved in lipid homeostasis and cholesterol biosynthesis. SREBP1 localizes in the nuclei in cells under both laminar and disturbed flows for 1 hour. After 12 hr, unlike disturbed flow, laminar flow leads to translocation of SREBP1 to the cytoplasm. | 2002 | [1] |
| Nuclear factor NF-kappa-B p105 subunit  *NFKB1* | 968 | Transcription factor involved in many biological processes. Cyclic tensile strain of low magnitude inhibits the IL-1b-induced nuclear translocation of the p65/p50 dimers of NF-kappa-B. | 2003 | [2-4] |
| Catenin beta-1  *CTNNB1* | 781 | Component of an E-cadherin/catenin adhesion complex. Also downstream component of the canonical Wnt signaling pathway. In the presence of Wnt ligand, CTNNB1 accumulates in the nucleus and acts as a coactivator for transcription factors of the TCF/LEF family, leading to activate Wnt responsive genes. Fluid shear stress in osteoblasts induces translocation of beta-catenin to the nucleus. | 2004 | [5-8] |
| Zyxin  *ZYX* | 572 | Adaptor protein at focal adhesion regulating cytoskeletal dynamics and signal transduction. Cyclic stretch, but not to osmotic induces dissociation of zyxin from focal adhesions and translocation to the nucleus. | 2004 | [9-11] |
| Myocardin-related transcription factor A *MRTFA* (*MAL*/*MKL1*) | 931 | Transcription coactivator that associates with the serum response factor (SRF) transcription factor to control expression of genes involved in development, morphogenesis and cell migration.  MRTFA binds G-actin that regulates activity of the MRTFA-SRF complex. Activity is also regulated by F-actin in the nucleus. Force application induces nuclear translocation of MRTF-A but not MRTF-B. | 2007 | [12-16] |
| Focal adhesion kinase 1  *PTK2* (*FAK*) | 1052 | Non-receptor protein-tyrosine kinase that regulates formation and disassembly of focal adhesion, cell migration, proliferation and apoptosis. After 30 min of 10% static strain FAK translocates to spots within and around the nuclei. | 2007 | [17] |
| Transcriptional coactivator YAP1  *YAP1* | 504 | YAP (Yes-associated protein) localization and activity are regulated by cell density via the Hippo pathway. | 2007 | [18] |
| Phosphorylated mitogen-activated protein kinase 3/1 (ERK1/2), mitogen-activated protein kinase 8/9 (JNK1/2), mitogen-activated protein kinase 11~14 (p38 MAPK)  *MAPK3/1*,  *MAPK8/9*,  *MAPK14* | 379/360  427/424  360~367 | Serine/threonine kinases in the MAP kinase signal transduction pathway. Low shear stress to endothelial cells induces phosphorylation and translocation of ERK1/2, p38 MAPK, and JNK1/2 from the cytoplasm into the nucleus. | 2008 | [19-22] |
| Notch intracellular domain | 2555 (intracellular domain : 802) | Receptor for membrane-bound ligands Jagged-1, Jagged-2, and Delta-1 to regulate cell-fate determination. Shear stress induces cleavage of Notch and translocation of the Notch intracellular domain into the nucleus. | 2009 | [23-26] |
| Transcriptional enhancer factor TEF-1/WW domain-containing transcription regulator protein 1  *TEAD1*/ *WWTR1*(*TAZ*) | 426  400 | TEAD1 is transcription factor which plays a key role in the Hippo signaling pathway. WWTR1 (TAZ) is a transcriptional coactivator that binds to TEAD1. Loss of cell-cell contact leads to nuclear translocation of TAZ and TEAD1 | 2010 | [27, 28] |
| Polycystin- 1  *PKD1* | 4303 (∼200 amino acid C-terminal cytoplasmic tail) | Form complex with PKD2 to act as a heteromeric calcium-permeable ion channel that is activated by a Wnt family member. Upon mechanical stimulation, the C-terminal cytoplasmic tail (CT) of PKD1 is proteolytically cleaved and released from the membrane, being translocated to the nucleus. Nuclear translocated CT interacts with several transcription factors such as AP-1 and STAT3. | 2010 | [29] |
| Zinc finger protein ZIC 1  *ZIC1* | 447 | Transcriptional activator. Fluid shear stress induces nuclear localization of Zic1 in osteocytes. | 2010 | [30] |
| Transcription factor Jun (Activator protein-1/  AP-1), transcription factor p65 (RelA/p65), and nuclear factor NF-kappa-B p105 subunit (cleaved into p50 subunit)  *JUN*  *NFKB1*  *RALA*  *NFKB1* | 331  551  968 (p50: 433) | Transcription factor that heterodimerizes with proteins of the FOS family to form an AP-1 transcription complex to induce transcription. Tensile force increases the nuclear translocation of c-Jun, RalA, and p50. | 2011 | [31] |
| Transcriptional coactivator YAP1/WW domain-containing transcription regulator protein 1  *YAP1*/ *WWTR1*(*TAZ*) | 504/400 | Transcriptional coactivator and corepressor in the Hippo signaling pathway. YAP/TAZ translocate between the nucleus and cytoplasm depending on substrate rigidity and actomyosin contraction. The translocation is also cell density-dependent. | 2011 | [32] |
| Glucocorticoid receptor  *NR3C1* | 777 | Transcription factor that binds to glucocorticoid response elements of nuclear and mitochondrial DNA. Shear stress induces nuclear translocation of glucocorticoid receptor. | 2012 | [33, 34] |
| Retinoic acid receptor gamma  *RARG* | 454 | Stiff substrates drive translocation of the transcription factor retinoic acid receptor gamma into the nucleus to regulate lamin A/C transcription. | 2013 | [35] |
| Runt-related transcription factor 2  *RUNX2* | 521 | Transcription factor involved in osteoblastic differentiation and skeletal morphogenesis. YAP and RUNX2 are located in the nuclei of hMSCs cultured on tissue culture polystyrene plates. YAP and RUNX2 are located in the cytoplasm of hMSCs cultured strictly on soft hydrogels. | 2014 | [36] |
| Mothers against decapentaplegic homolog 1/5/8, 2/3  *SMAD1/5/8, 2/3* | 465/465/467  467/425 | Transcriptional modulator. Substrate rigidity regulates nucleocytoplasmic shuttling of SMADs. | 2014 | [37] |
| Twist-related protein 1  TWIST1 | 202 | Acts as a transcriptional regulator. Inhibits myogenesis by sequestrating E proteins, inhibiting Transcriptional regulator. Matrix stiffness promotes nuclear translocation of TWIST1 by releasing TWIST1 from G3BP2 in the cytoplasm. | 2015 | [38] |
| Oligodendrocyte transcription factor 1, Oligo1, Class B basic helix-loop-helix protein 6 (bHLHb6), Class E basic helix-loop-helix protein 21 (bHLHe21)  OLIG1, BHLHB6, BHLHE21 | 271 | Oligodendrocyte transcription factor 1 (Olig1) is a key regulator of oligodendrocyte development and translocated to the nucleus on stiff but not on soft substrates. During oligodendrocyte differentiation, Olig1 is phosphorylated and translocated from the nucleus to the cytoplasm. Olig1 cytoplasmic localization depends on its phosphorylation on serine 138 by PKA. | 2016 | [39] |
| Four and a half LIM domains protein 2  FHL2 | 279 | Transcriptional coactivator and a scaffold protein in cell adhesions. Matrix mechanics regulates nucleocytoplasmic shuttling of FHL2. Unlike YAP1, soft substrates stimulate FHL2 transport to the nucleus. | 2016 | [40] |
| Histone deacetylase 4  HDAC4 | 1084 | Deacetylate lysine residues on the core histones (H2A, H2B, H3 and H4) to regulate epigenetic changes in transcriptional regulation.  Mechanical compression induces HDAC4 nuclear import. | 2016 | [41] |
| NADPH oxidase 4  NOX4 | 578 | Produce superoxide in the nucleus and regulate gene expression. Luminal flow induces Nox4 translocation to the nucleus. | 2016 | [42] |
| Cytosolic phospholipase A2 (cPLA2)  PLA2G4A | 749 | Calcium-dependent phospholipase and lysophospholipase. Osmotic swelling of cells and their nuclei activates cPla2 by translocating it from the nucleoplasm to the nuclear envelope. | 2016 | [43] |
| Merlin  *NF2* | 595 | Tumor suppressor protein that interacts with E-cadherin and F-actin. At low cell density, merlin is associated with E-cadherin. At high density, contraction of the circumferential actin belt releases merlin from E-cadherin and then merlin is imported into the nucleus to export nuclear YAP/TAZ into the cytoplasm. | 2017 | [44] |
| Cardiac-specific transcription factors GATA4, MEF2C, and NKX2-5  *GATA4*  *MEF2C*  *NKX2-5* | 442  473  324 | Tensile strain induces translocation of cardiac-specific transcription factors GATA4, MEF2C and Nkx2.5, and induced expression of the sarcomeric actin and cardiac troponin T proteins. | 2017 | [45] |
| Phosphorylated signal transducer and activator of transcription 3  *STAT3* | 770 | Signal transducer and transcription activator. Mechanical stretching induces interaction of cleaved C-terminal tail of PKD1 with phosphorylated JAK2 in human osteoblastic cells. The active JAK2 phosphorylates STAT3 (active) that translocates to the nucleus to induce gene expression. | 2017 | [46] |
| Histone acetyltransferase p300  *EP300* | 2414 | Histone acetyltransferase that regulates transcription by remodeling chromatin. Substrate stiffness regulates AKT signaling via RhoA to induce phosphorylation of p300 that translocates to the nucleus in Hepatic stellate cells. | 2018 | [47] |
| EH domain-containing protein 2  *EHD2* | 543 | ATPase that binds membrane. cyclic stretching and hypo-osmotic shock induce release of EHD2 from caveolae, SUMOylation, and translocation to the nucleus to regulate gene expression. | 2018 | [48] |
| Caveolae-associated protein 1 *CAVIN1* | 390 | Core component of the CAVIN in the caveolae. Also called polymerase I and transcript release factor that promotes ribosomal RNA transcription. Mild hypo-osmotic stress induces translocation of a large portion of the plasma membrane GFP-cavin-1 to the cytosol and the nucleus. | 2019 | [49] |
| ANKHD1 and ANKRD17 |  | Mask family proteins contain two ankyrin repeat domains that bind Yki/YAP as well as a conserved nuclear localisation sequence (NLS) and nuclear export sequence (NES), suggesting a role in nucleo-cytoplasmic transport. | 2019 | [50] |
| X-box-binding protein 1, interferon regulatory factor 1  *XBP1*, *IRF1* | 261  325 | Transcription factors. Low shear stress induces temporal rise in p38 phosphorylation that activates the nuclear translocation of XBP1 and IFN regulatory factor 1. | 2019 | [51] |
| Histone-lysine N-methyltransferase SMYD3  *SMYD3* | 428 | Methylates Lys-4 of histone H3, inducing di- and tri-methylation, but not monomethylation. Also methylates Lys-5 of histone H4. Unlike YAP/TAZ, disruption of actomyosin contraction promote nuclear localization of SMYD3. | 2020 | [52] |
| Fermitin family homolog 2 (Kindlin-2)  *FERMT2* | 680 | Scaffolding protein that enhances integrin activation mediated by talins. Stressing fibroblasts using ferromagnetic microbeads, stretchable silicone membranes, and cell contraction induced by PAR-1 agonist promote nuclear translocation of kindlin-2. | 2020 | [53] |
| Lipoma preferred partner  LPP | 612 | The nearest relative of zyxin among the Lin11-Isl1-Mec3 (LIM) domain-containing proteins. Similar to zyxin, LPP is localized to focal adhesions and cell–cell junctions. Upon exposure of cells to biomechanical deformation, LPP only transiently translocates to the nucleus to function as a transcriptional co-activator. | 2021 | [54, 55] |
| Importin 7  *IPO7* | 1038 | Ran-dependent nuclear transport receptor. Form YAP/Imp7 complex to respond to mechanical cues. YAP is as a dominant cargo of Imp7, restricting the Imp7 binding to other Imp7 cargoes such as Smad3 and Erk2. | 2022 | [56] |
| Ubiquitin-conjugating enzyme E2 A/B  *UBE2A/B (RAD6A/B)* | 152 | Ubiquitin-conjugating enzyme E2 that regulates transcription by catalyzing the monoubiquitination of histone H2B at 'Lys-120' to form H2BK120ub1. Cell density- and force-dependent nucleocytoplasmic translocation. | 2023 | [57] |
| Mothers against decapentaplegic homolog 4  SMAD4 | 552 | Component of the heterotrimeric SMAD2/SMAD3/SMAD4 complex that forms in the nucleus to stimulate transcription. Translocate from the nucleus to the cytosol at high-density. | 2023 | [58] |
| Prostaglandin E synthase 3  *PTGES3* | 160 | Molecular chaperone that localizes to genomic response elements in a hormone-dependent manner and disrupts receptor-mediated transcriptional activation. Translocate from the nucleus to the cytosol at high-density. | 2023 | [58] |
| Protein mono-ADP-ribosyltransferase TIPARP  *TIPARP* | 657 | ADP-ribosyltransferase that mediates mono-ADP-ribosylation of aspartate, cysteine, and glutamate residues on target proteins. Negative regulator of aryl hydrocarbon receptor (AHR), a ligand-activated transcription factor, by mediating mono-ADP-ribosylation of AHR, leading to inhibit AHR activity. Translocate from the nucleus to the cytosol at high-density. | 2023 | [58] |
| Core-binding factor subunit beta  *CBFB* | 182 | Forms the heterodimeric complex core-binding factor (CBF) with RUNX family proteins (RUNX1, RUNX2, and RUNX3). RUNX members modulate the transcription of their target genes. Translocate from the nucleus to the cytosol at high-density. | 2023 | [58] |

\* In chronological order.

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