Table S1. Summary of post-transcriptional mechanisms and their effects on pluripotent, somatic and malignant stem cells.

EFFECTS ON PLURIPOTENT STEM CELLS	EFFECTS ON SOMATIC STEM CELLS	EFFECTS ON CANCER STEM CELLS
RNA SPLICING **Can produce distinct protein isoforms, introduce premature stop codons and cause UTR variation. Can also affect protein structure, function, mRNA stability, subcellular localization and translation efficiency.**		
Splicing factor SRSF2 promotes hESC self-renewal directly by promoting the expression of *OCT4* and *NANOG* (Lu et al., 2014) MBNL splicing factors disrupt hESC self-renewal by repressing hESC-specific isoforms that promote the expression of *OCT4, SOX2,* and *NANOG* (Gabut et al., 2011)	Sustains self-renewal in HSCs by generating distinct *HMGA2* mRNA isoforms that escape miRNA-mediated repression (Cesana et al., 2018)	Cancer stem cells adopt splicing patterns similar to those of undifferentiated stem cells (Crews et al., 2016; Sebestyen et al., 2016) Breast cancer stem cells undergo CD44 isoform switching (Zhang et al., 2019) Chronic myeloid leukemia blast crisis stem cells express high levels of hESC-associated CD44 isoforms (Holm et al., 2015) GSK3β mis-splicing and BCL2 splice variants promote leukemia stem cell self-renewal and survival (Abrahamsson et al., 2009; Goff et al., 2013) Splicing factors can be mutated or epigenetically modified in pre-leukemic and leukemic disorders (Ogawa, 2014; Yoshida and Ogawa, 2014)
RNA METHYLATION **m6A Modifications: Can promote the stability and cap dependent translation of m^6A modified mRNA. Can also suppress translation by promoting mRNA decay.**		
Enhances ESC self-renewal and somatic cell reprogramming by stabilizing transcripts of core pluripotency factors (Chen et al., 2015; Geula et al., 2015) Supports differentiation by promoting the degradation of	Maintains HSC number and reconstituting activity in adult mice by mediating c-Myc translation (Lee et al., 2019) Promotes hematopoietic specification in zebrafish embryos through YTHDF2-mediated repression of	High expression of *METTL3* supports leukemia stem cell survival (Barbieri et al., 2017; Vu et al., 2017; Weng et al., 2018) High expression of *FTO* promotes cell survival in cervical cancer and acute

pluripotency transcripts (Wang et al., 2014b)	transcripts (Zhang et al., 2017) Supports osteogenic differentiation of skeletal stem cells by enhancing the translational efficiency of *Pthr1* (Wu et al., 2018)	myeloid leukemia (King et al., 2016; Li et al., 2017b)
m5C Modifications: Can support ribosome biogenesis and polysome assembly, increase translation fidelity, and stabilize tRNA.		
	Promotes translation and differentiation of epidermal stem cells by preventing the accumulation of tRNA-derived small noncoding RNA (Blanco et al., 2016)	
m1A Modifications: Can increase tRNA and rRNA stability and the translational efficiency of mRNA.		
PSEUDOURIDYLATION **Can enhance tRNA stability and codon base-pairing, and alter translation termination.**		
PUS7 supports germ layer specification of hESCs (Guzzi et al., 2018) *PUS7* supports activation of tRNA-derived fragments required for translational control in hESCs (Guzzi et al., 2018)	*PUS7* supports the translational program required for commitment of $CD34^+$ human hematopoietic and stem progenitor cells (Guzzi et al., 2018)	
RNA EDITING **Can alter mRNA coding or UTR sequence and can support miRNA biogenesis.**		
Influences the efficiency of reprogramming (Germanguz et al., 2014)	ADAR1 regulates quiescence and cell cycle entry of human hematopoietic stem and progenitor cells (Jiang et al., 2019) Adar1 supports multilineage reconstituting activity of mouse HSCs (Orkin and Zon, 2008; XuFeng et al., 2009) Adar1 regulates apoptosis and growth of $Lgr5^+$ intestinal stem cells (Qiu et al., 2013)	Editing of mRNAs encoding *GLI1*, *GSK3β*, *AZIN1* and *APOBEC3D* are required for survival of leukemia stem and progenitor cells (Crews et al., 2015) ADAR-1mediated editing stabilizes *MDM2*, which increases MDM2 and enhances p53 degradation within leukemia stem cells (Jiang et al., 2019) *PTPN6* editing abrogates splicing and supports leukemogenesis in acute myeloid leukemia (Beghini et al., 2000)

MICRO RNA (MIRNA) **Repress gene expression by promoting degradation of mRNA**		
DGCR8 and Dicer1 support differentiation of mouse ESCs (Kanellopoulou et al., 2005; Wang et al., 2007) Supports human and mouse ESC differentiation by suppressing expression of pluripotency genes *Oct4, Sox2, Klf4*, and *Nanog* (Tay et al., 2008; Wang et al., 2017c; Xu et al., 2009b) Increases reprogramming efficiency of iPSCs (Li et al., 2011; Lin et al., 2008)	miR-128 and miR-181 inhibit HSC differentiation into hematopoietic lineages (Georgantas et al., 2007) miR206 represses Pax3, which promotes muscle stem cell activation (de Morree et al., 2019) miR124 and miR128 are specifically expressed in neuronal lineages (Smirnova et al., 2005) Astrocytes specifically express miR-26, miR-23, and miR-29 (Smirnova et al., 2005)	Germline and somatic mutations in *DICER1* predispose individuals to cancer (Foulkes et al., 2014) Impaired Dicer1 function promotes colon cancer and endometrial cancer stemness (Iliou et al., 2014; Wang et al., 2017b) Several cancer types have a defect in miRNA biogenesis and exhibit a global downregulation of miRNA production (Calin and Croce, 2006; Gaur et al., 2007; Lu et al., 2005) Breast cancer, colon cancer, pancreatic cancer, neuroblastoma, hepatocellular carcinoma, and non-small-cell lung cancer downregulate miR-34a (Asadzadeh et al., 2019) miR-34a inhibits prostate cancer stem cell expansion by suppressing CD44 expression (Liu et al., 2011) miR-34a inhibits self-renewal of breast cancer stem cells (Ma et al., 2015)
PROTEIN SYNTHESIS **mTOR Activation: Promotes cap-dependent translation through phosphorylation of S6K and 4E-BP1.**		
Helps maintain a chromatin landscape that allows for transcription of developmental genes in mouse ESCs (Bulut-Karslioglu et al., 2018)	Depletes HSCs and impairs HSC serial reconstituting capacity by increasing the rate of protein synthesis (Signer et al., 2014; Yilmaz et al., 2006; Zhang et al., 2006)	Deletion of *Pten* promotes the generation of leukemia-initiating cells (Yilmaz et al., 2006) Loss of function mutations in *PTEN* have been identified in prostate cancer, glioblastomas, carcinomas, and hematopoietic

		malignancies (Milella et al., 2015) S6K1 is overexpressed in breast, lung, and ovarian cancers, and is correlated with poor prognosis in hepatocellular carcinomas and prostate cancer (Pópulo et al., 2012) eIF4E is overexpressed in colon, head and neck, and breast cancers, as well as thyroid carcinoma and non-Hodgkin's lymphomas (Pópulo et al., 2012)
Translational Apparatus: Can enhance protein synthesis by promoting ribosome loading onto mRNA, polysome formation, and through the use of different translational start sites.		
Can control global translational output in ESCs through ribosome pausing and the use of translation start sites from upstream open reading frames or non-conventional start sites (Ingolia et al., 2011; Sampath et al., 2008) Can increase translational output during ESC differentiation by increasing polysome abundance and the efficiency of ribosome loading (Ingolia et al., 2011; Sampath et al., 2008)	HSCs, muscle satellite cells, germline stem cells and quiescent neural stem cells exhibit low protein synthesis (Llorens-Bobadilla et al., 2015; Sanchez et al., 2016; Signer et al., 2014; Zismanov et al., 2016) Modest increases or decreases in protein synthesis impair HSC self-renewal and reconstituting activity (Goncalves et al., 2016; Signer et al., 2014)	
MECHANISMS OF TRANSLATIONAL CONTROL **Poly(A)-Binding Proteins: Initiate translation by binding poly(A) tails and interacting with translation initiation factors**		
Can increase global translation rates in ESCs through interactions with DAZL transcripts (Sampath et al., 2008)	Supports the proliferation of germline stem cells during *C. elegans* development (Ko et al., 2010)	
Eif4e Binding Proteins: Suppress cap-dependent translation		
Supports mouse ESC pluripotency by suppressing	Deletion of 4E-BPs modestly increases protein synthesis	

the translation of Yy2 (Tahmasebi et al., 2016) Compound deletion of 4E-BPs and p53 enhances iPSC generation (Tahmasebi et al., 2014)	within HSCs and impairs their serial reconstituting activity (Signer et al., 2016) Impairs neural stem cell self-renewal (Hartman et al., 2013)	
tiRNA Biogenesis: Suppresses translation by RNA interference or displacement of translation initiation factor eIF4G.		
	Angiogenin in the bone marrow microenvironment restricts protein synthesis within HSCs, which increases HSC cycling and diminishes reconstituting activity (Goncalves et al., 2016; Signer et al., 2014)	
Cap-Independent Translation: Translation of mRNA that does not require interaction of mRNA with initiation factors eIF4E and/or eIF4G		
Promotes differentiation of human and mouse ESCs (Sugiyama et al., 2017; Yamanaka et al., 2000; Yoffe et al., 2016)		
RIBOSOME BIOGENESIS & ASSEMBLY **Ribosomal Gene Mutations: Can impair ribosome biogenesis and reduce translation.**		
	Impairs human hematopoietic stem and progenitor cell lineage commitment by altering the translation of *GATA1* (Khajuria et al., 2018)	Mutations in *Rpl24* slow the progression of *Myc*-driven B cell malignancies and T cell neoplasms driven by *Pten* deletion (Barna et al., 2008) Ribosomal mutations can predispose patients to myelodysplastic syndrome and acute myeloid leukemia (Goudarzi and Lindström, 2016)
Ribosome Biogenesis Factors: Support translation by processing rRNA and ribosomal proteins.		
Htatsf1 supports mouse ESC self-renewal and differentiation by regulating the levels of pluripotency factors (Corsini et al., 2018)	Nle reduces HSC regenerative capacity (Le Bouteiller et al., 2013)	
Small Subunit Processome: Supports translation by processing 18S rRNA.		
Maintains mouse ESC pluripotency by supporting the		

translation of pluripotency factors (You et al., 2015)		
PROTEIN QUALITY CONTROL **ER Unfolded Protein Response: Alleviates the accumulation of unfolded proteins in the ER by attenuating protein synthesis, inducing expression of folding chaperones, and, in some cases, inducing apoptosis.**		
Pharmacologic activation promotes endodermal and mesodermal specification in ESCs (Kroeger et al., 2018; Wang et al., 2015a; Xu et al., 2014) Pharmacologic activation enhances reprogramming efficiency of somatic cells (Simic et al., 2019)	Maintains muscle stem cell identity by suppressing the translation of myogenesis-related transcripts (PERK) (Alter and Bengal, 2011; Zismanov et al., 2016) Supports mouse intestinal stem cell differentiation (PERK) (Heijmans et al., 2013) Induces apoptosis in HSCs during conditions of extreme stress (PERK) (Liu et al., 2019; van Galen et al., 2018) Reduces growth of *Drosophila* intestinal stem cells (IRE1) (Niederreiter et al., 2013; Wang et al., 2014a) Promotes mouse HSC survival and recovery after irradiation (IRE1) (Chapple et al., 2018; Liu et al., 2019) Enhances engraftment of HSCs and survival of primitive cord blood stem and progenitor cells (ATF4) (van Galen et al., 2018)	Enhanced UPR^{ER} activation can sensitize colon cancer stem cells to chemotherapy (Wielenga et al., 2015) Nras with the G12D mutation hyperactivates IRE1 in pre-leukemic stem cells and enhances HSC reconstitution (Liu et al., 2019; van Galen et al., 2014)
Mitochondrial Unfolded Protein Response: Upregulates mitochondrial chaperones and proteases in response to accumulation of unfolded proteins in the mitochondria.		
	Supports HSC quiescence and regenerative capacity (Mohrin et al., 2015) Helps maintain stemness of intestinal stem cells (Berger et al., 2016)	

Heat Shock Response: Maintains cytosolic proteostasis through the coordination of heat shock proteins that facilitate protein folding, trafficking, and degradation.		
Promotes hESC differentiation by repressing *OCT4* expression (Byun et al., 2013) Mouse ESCs downregulate expression of Hsp70 during differentiation into embryoid bodies and neural precursors (Battersby et al., 2007; Saretzki et al., 2004)	Hsp70 helps control hematopoietic progenitor numbers in zebrafish and prevent apoptosis in human erythroid precursors (Craven et al., 2005; Ribeil et al., 2007) Small heat shock proteins have elevated expression during myoblast differentiation (Sugiyama et al., 2000)	HSF1 is overexpressed or amplified in prostate adenocarcinomas, squamous cell carcinomas, hepatocellular carcinoma, and pancreatic cancer (Dai et al., 2012) HSF1 can support malignant phenotypes in breast tumors and T cell leukemia (Dai et al., 2012) HSP90 supports the folding of proteins involved in signaling pathways dysregulated in cancer (Ak2, Her2, HIF-1α) and mutant proteins (v-Src, Bcr-Abl, and p53) and is associated with poor prognosis in lung cancer, melanoma, and leukemia (Chatterjee and Burns, 2017) Overexpression of HSP70 and HSP27 can inhibit programmed cell death and is associated with poor prognosis in myelodysplastic syndrome, melanoma, colon, breast, endometrial, oral, skin, liver, and lung cancers (Chatterjee and Burns, 2017)
UBIQUITIN PROTEASOME SYSTEM **Controls the content and quality of the proteome through the turnover of proteins and degradation of misfolded proteins.**		
Wwp2 supports ESC function by ubiquitinating and targeting Oct4 for degradation (Xu et al., 2009a; Xu et al., 2004) Fbxw7 promotes ESC differentiation by ubiquitinating and targeting c-Myc for degradation (Szutorisz et al., 2006) High levels of proteasome activity promote ESC function	Fbxw7 promotes HSC self-renewal by ubiquitinating and targeting c-Myc for degradation (Reavie et al., 2010; Thompson et al., 2008; Wilson et al., 2004) Huwe1 prevents HSC exhaustion by reducing the abundance of N-Myc (King et al., 2016)	Low proteasome activity is a feature of cancer stem cells (Munakata et al., 2016; Pan et al., 2010; Vlashi et al., 2009) Glioma, breast cancer, lung carcinoma, and colorectal cancer cell lines that exhibit low proteasome activity have stem-like phenotypes and are more tumorigenic (Munakata et al., 2016; Pan et al., 2010; Vlashi et al., 2009)

by regulating the abundance of Oct4 and Nanog (Buckley et al., 2012)	The proteasome controls the abundance of regulators of HSC self-renewal including p53, Hif1α, Notch, Stat5 (Moran-Crusio et al., 2012) Rpt3 supports muscle stem cell quiescence, differentiation, and regeneration in response to injury (Kitajima et al., 2018)	