Chapter 2

Molecular mechanisms of mTOR regulation by stress

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Abstract

Tumors are prime examples of cells that grow in unfavorable environments eliciting cellular stress. The high metabolic demand of tumors and their insufficient vascularization cause deficiency of oxygen and nutrients. Moreover, oncogenic mutations map to signaling events via mechanistic/ mammalian target of rapamycin (mTOR), metabolic pathways, and mitochondrial function. These alterations have been linked with cellular stresses, in particular endoplasmic reticulum (ER) stress, hypoxia, and oxidative stress. Yet, tumors survive these challenges and acquire highly energy demanding traits, such as overgrowth and invasiveness. In this review we focus on stresses that occur in cancer cells and discuss them in the context of mTOR signaling. Of note, many tumor traits require mTOR complex 1 (mTORC1) activity, but mTORC1 hyperactivation eventually sensitizes cells to apoptosis. Thus, mTORC1 activity needs to be balanced in cancer cells. We provide an overview of mechanisms contributing to mTOR regulation by stress, and suggest a model wherein stress granules (SG) function as guardians of mTORC1 signaling allowing cancer cells to escape stress-induced cell death.

1. Why do cancer cells profit from mTOR activation?

The mTOR signaling network (**Fig. 1**) is hyperactivated in many tumors (reviewed by Yecies et al. (2011)). mTOR kinase occurs in two multiprotein complexes, mTORC1 and mTORC2 (Shimobayashi and Hall, 2014). mTORC1 functions as a master regulator of cell growth and metabolism by favoring anabolic processes in the presence of nutrients and energy. mTORC1 contains the essential specific scaffold protein regulatory associated protein of mTOR (raptor) (Hara et al., 2002; Kim et al., 2002) whereas mTORC2 contains the specific proteins rapamycin-insensitive companion of mTOR (rictor) and mammalian stress-activated protein kinase interacting protein 1 (mSIN1) (reviewed by Shimobayashi et al. (2014)). mTORC2 senses nutrients and growth factors and modulates for example lipid and glucose metabolism (Hagiwara et al., 2012) ,and cytoskeleton reorganization (reviewed by Oh et al. (2011)). The cancer drug rapamycin directly binds and inhibits mTORC1, but can also have indirect long term effects on mTORC2 (Lamming et al., 2012; Sarbassov et al., 2006).

Amino acids activate mTORC1 via the rag GTPases (Kim et al., 2008; Sancak et al., 2008), which modulate in conjunction with the guanine nucleotide exchange factor (GEF) ragulator complex (Bar-Peled et al., 2012) and the GTPase activating protein (GAP) folliculin (FLCN) (Tsun et al., 2013) the translocation of mTORC1 to the lysosomal membrane, in a glutaminolysis dependent manner (Duran et al., 2012) (reviewed by Bar-Peled et al. (2014)). At the lysosome, mTORC1 encounters the small GTPase ras-homologue-enriched-in-brain (rheb), which activates mTORC1 in response to growth factors (insulin) (Long et al., 2005). Amino acids deprivation, in a rag GTPase dependent manner, leads to recruitment of the hamartin (TSC1) – tuberin (TSC2) heterocomplex (TSC1-TSC2) to the lysosomal membrane (Demetriades et al., 2014). The tumor suppressor TSC1-TSC2 functions as a GAP for the GTPase rheb and thereby inhibits mTORC1 (Inoki et al., 2003a).

The insulin receptor (IR), via insulin receptor substrate (IRS), activates class I phosphatidylinositol 3-kinases (PI3K) whose subunits are often mutated in tumors. PI3K phosphorylates phosphatidylinositol-4,5-biphosphate (PIP2) to generate phosphatidylinositol-3,4,5-triphosphate (PIP3). PIP3 binding to the oncogenic kinase Akt (also termed protein kinase B, PKB) and 3-phosphoinositide-dependent kinase-1 (PDK1) enables their translocation to the plasma membrane, where PDK1 phosphorylates and activates Akt. Akt acts as an inhibitor of the

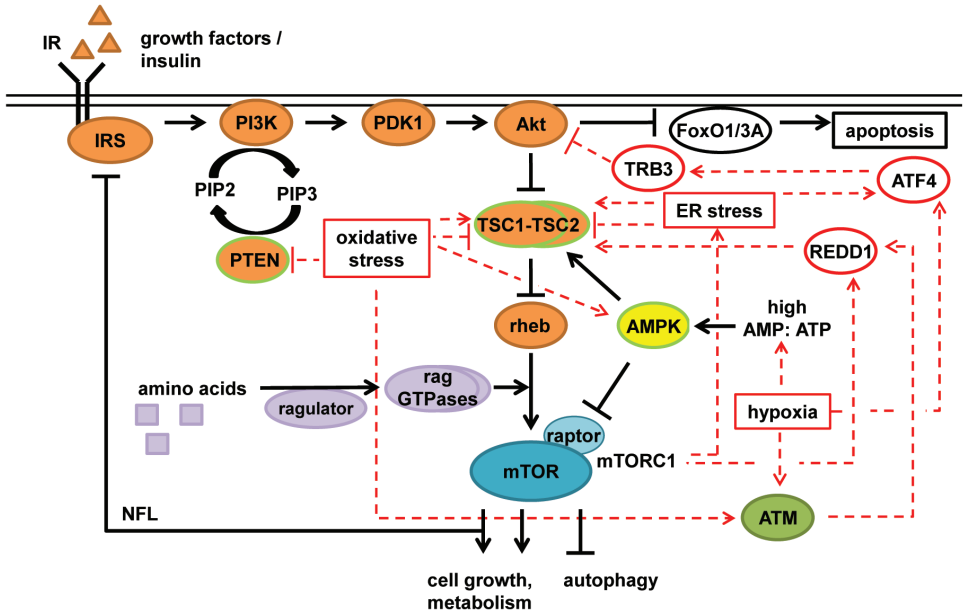

Figure 1. mTORC1 and stress. mTORC1 is regulated by amino acids, growth factors (i.e. insulin) and energy status (AMP:ATP). amino acids are sensed by the ragulator complex and the rag GTPases mediating mTORC1 re-localization to lysosomes, where mTORC1 encounters rheb. Insulin activates the IR which then recruits IRS. IRS induces PI3K which converts PIP2 to PIP3. PIP3 accumulation results in the recruitment of PDK1 and Akt to the plasma membrane. Here, Akt is activated by PDK1. Akt phosphorylates and inhibits the TSC1-TSC2 complex, which inhibits rheb. Akt also inhibits the FoxO1/3A transcription factors which positively regulate apoptosis. AMPK is activated by high AMP:ATP and inhibits mTORC1 by activating TSC1-TSC2 as well as by direct phosphorylation of the mTORC1 component raptor. Activation of mTORC1 inhibits IRS and Grb10 (not shown), resulting in negative feedback regulation of the PI3K-Akt branch. mTORC1 hyperactivation can lead to ER stress. ER stress can activate or inhibit the TSC1-TSC2 complex. In addition, ER stress induces ATF4 translation which can induce expression of the negative Akt regulator TRB3. Hypoxia induces ATF4 translation as well, and activates AMPK. Hypoxia induced HIFs (via ATM) induce REDD1 expression, which activates the TSC1-TSC2 complex, inhibiting mTORC1. This results in a NFL, as mTORC1 controls REDD1 stability. Oxidative stress inhibits the tumor suppressors PTEN, and inhibits or activates TSC1-TSC2. Furthermore, oxidative stress can activate ATM and AMPK, both of which inhibit mTORC1. Tumor suppressors are framed in green. Stress inputs are shown in red.

TSC1-TSC2 complex by phosphorylating TSC2. TSC2 phosphorylation by Akt leads to dissociation of the TSC1-TSC2 complex from the lysosomes (Menon et al., 2014), and enables mTORC1 activation. The PI3K antagonist phosphatase and tensin homolog (PTEN) is a tumor suppressor and it counteracts growth factor dependent mTORC1 activation by dephosphorylating PIP3 to generate PIP2 (reviewed e.g. by Laplante et al. (2012)).

mTORC1 responds to cellular energy via the heterotrimeric AMP-activated protein kinase (AMPK). AMPK is activated by two mechanisms. On the

one hand, kinases such as the tumor suppressor kinase LKB1 and calmodulin-dependent protein kinase kinase beta (CaMKKbeta) phosphorylate AMPK in its activation loop. Furthermore, when the cellular ATP:AMP ratio is low, AMP directly binds to AMPK and allosterically activates it (reviewed by Hardie et al. (2014)). AMPK inhibits mTORC1 by phosphorylating raptor (Gwinn et al., 2008), and by an activating phosphorylation on TSC2 (Inoki et al., 2003b). Furthermore, the ATP sensitive Tel2-Tti1-Tti2 (TTT)-RUVBL1/2 complex activates mTORC1 by favoring mTORC1 assembly and its lysosomal localization in a rag GTPase dependent manner (Kim et al., 2013).

Cancer cell growth depends on ATP-demanding anabolic processes including protein, lipid, and nucleotide biosynthesis. mTORC1 controls ATP supply by inducing mitochondrial biogenesis, tricarboxylic acid (TCA) cycle, and aerobic respiration (Cunningham et al., 2007; Morita et al., 2013; Schieke et al., 2006). Furthermore, mTORC1 promotes the delivery of substrates to the TCA cycle by inducing glucose uptake (Buller et al., 2008) and glutamine catabolism (Csibi et al., 2013). A major anabolic function of mTORC1 in cancer is its stimulating role in translation (Hsieh et al., 2012) (reviewed by Ma and Blenis (2009)). mTORC1 phosphorylates and inhibits eukaryotic translation initiation factor 4E-binding protein 1 (4E BP1), an inhibitor of 5' cap dependent translation. Phosphorylation of 4E-BP1 decreases its binding to the eIF4F complex component eukaryotic translation initiation factor 4E (eIF4E), which upon release from 4E-BP1 assembles into the eIF4F complex. The eIF4F complex mediates the scanning process via which ribosomes reach the start codon. Furthermore, mTORC1 enhances the cellular protein biosynthesis capacity by activating ribosomal RNA (rRNA) transcription and processing (Iadevaia et al., 2012c) (reviewed by Iadevaia et al. (2012a)), and biosynthesis of ribosomal proteins and elongation factors: these proteins are often encoded by transcripts that contain 5' terminal oligopyrimidine (5'TOP) tracts (Levy et al., 1991), whose translation depends on 4E-BP1 inactivation (Morita et al., 2013; Thoreen et al., 2012). In addition, the raptor interacting protein La-related protein 1 (LARP1) binds to the mRNA 5'cap in an mTORC1 dependent manner, which seems to particularly affect translation of RNAs containing 5'TOP motifs (Tcherkezian et al., 2014). Furthermore, 5'TOP regulation by mTOR has been reported to also occur in a 4E-BP1 and mTORC1 independent manner (Miloslavski et al., 2014; Patursky-Polischuk et al., 2009), in particular under hypoxic conditions (Miloslavski et al., 2014). S6 kinase (S6K), another mTORC1 substrate, phosphorylates S6 (Chung et al., 1992) and the eIF4F component eukaryotic translation initiation factor 4B (eIF4B) (Kroczynska

et al., 2009; Raught et al., 2004), which may contribute to translational control by mTORC1, yet not by translational regulation of 5'TOP mRNAs (Tang et al., 2001). In addition, S6K promotes mRNA expression of ribosome biogenesis genes thereby likely increasing overall translation capacity (Chauvin et al., 2014). The PI3K-Akt-mTORC1 pathway upregulates the synthesis of lipids via the sterol regulatory element-binding protein (SREBP transcription factors) (Duvel et al., 2010; Hagiwara et al., 2012; Porstmann et al., 2005; Porstmann et al., 2008; Yecies et al., 2011), which regulate genes involved in lipid and sterol synthesis (Jeon and Osborne, 2012). mTORC1 stimulates nucleotide biosynthesis via direct phosphorylation of the trifunctional enzyme CAD (carbamoyl-phosphate synthetase 2-aspartate transcarbamylase-dihydroorotase), which catalyzes the first three steps of de novo pyrimidine synthesis (Ben-Sahra et al., 2013; Robitaille et al., 2013). In addition, mTORC1 promotes expression of genes encoding enzymes of the oxidative branch of the pentose phosphate pathway (PPP) (Duvel et al., 2010), which generates ribose-5-phosphate (R5P) and NADPH for biosynthesis. R5P and ATP are needed for the synthesis of 5-phosphoribosyl-1-phosphate which is required for the synthesis of purines and pyrimidines. Hence, cancer cells likely profit from mTORC1 activation, as this promotes building block biosynthesis and thereby contributes to abnormal proliferation. It needs to be noted though that mTORC1 inhibits the oncogene Akt via IRS (Harrington et al., 2004; Myers et al., 1994; Shah et al., 2004) and growth factor receptor-bound protein 10 (Grb10) (Hsu et al., 2011; Yu et al., 2011) dependent negative feedback loops (NFLs). Akt inhibits apoptosis, by inhibiting the transcription factor forkhead box O1/3A (FoxO1/3A) (Brunet et al., 1999). Furthermore, Mounir et al. (2011) have shown that Akt directly phosphorylates and inhibits the ER stress sensor protein kinase RNA-like ER kinase (PERK), thereby preventing its hyperactivation and subsequent cell death. Thus, chronic mTORC1 activation via NFLs results in Akt inhibition and thereby facilitates apoptosis (reviewed by Apenzeller-Herzog and Hall (2012)). Consequently, cancer cells need to balance mTORC1 activity to keep biosynthetic processes and Akt active at the same time.

2. mTOR regulation by stresses in cancer cells

The capacity of uncontrolled cellular growth and proliferation brings about different challenges, i.e. stresses, which a tumor cell has to cope with to achieve its survival. Nutrient and oxygen depletion in conjunction with a hyperactive metabolism, mitochondrial dysfunction, and oncogenic mTOR signaling are

common conditions in cancer cells (Cornu et al., 2013; Kumimoto et al., 2004; Liang and Mills, 2013; Modica-Napolitano and Singh, 2004; Wilson and Hay, 2011) and often correlate with cellular stresses. We focus here on ER stress, hypoxia, and oxidative stress and their interaction with mTOR and cancer cell metabolism (**Fig. 1**).

2.1. mTORC1 under ER stress

Numerous studies report on an accelerated unfolded protein response (UPR) in cancer cells. ER stress results from imbalances between protein synthesis and protein folding capacity leading to the accumulation of unfolded proteins in the ER lumen (reviewed by Clarke et al. (2014), Fels and Koumenis (2006)). Several factors can contribute to the phenomenon of ER stress (**Fig. 2**): when tumors outgrow the vascular system they eventually face a shortage in oxygen and nutrients (Brahimi-Horn et al., 2007; Fels and Koumenis, 2006). Decreased glucose supply restricts ATP synthesis, which is required for chaperone activity in the ER (reviewed by Braakman and Hebert (2013)). Thus, decreased ATP levels can result in impaired protein folding and ER stress. Glucose is not only used for ATP synthesis but is also a major source of carbon molecules for the synthesis of cellular building blocks (lipids, nucleotides, amino acids). Proliferating cells require lipids for membrane formation and ER expansion. Lipid shortage and hence reduced membrane synthesis can induce ER stress (Little et al., 2007; Schuck et al., 2009; van der Sanden et al., 2003) and apoptosis (Mashima et al., 2009; Pizer et al., 1996). These observations suggest that glucose limitation is a trigger for ER stress. However, studies on cancer metabolism report on the Warburg effect, i.e. aerobic glycolysis and accumulation of lactate (Cantor and Sabatini, 2012; Warburg, 1956). The Warburg effect is defined by an enhanced glycolytic rate under normoxic condition. Cells that exhibit the Warburg effect consume glucose relatively fast and therefore require a sufficient supply of glucose (Koppenol et al., 2011). These two seemingly contradictory views on glucose levels in cancer cells may be relevant at different stages of tumor progression. In the initial stages, increased levels of glucose transporters (Szablewski, 2013; Young et al., 2011) allow the cell to take up as many nutrients as the environment allows. Enhanced glucose uptake, in conjunction with the hyperactivation of the mTOR pathway, is prone to induce ER stress, as increased protein synthesis can overwhelm the protein folding capacity of the ER (Clarke et al., 2014; Ozcan et al., 2008). In contrast, at advanced tumor stages, the outgrowth from

the vascular system results in nutrient shortage, also leading to ER stress, as discussed earlier.

The ER has its own sensors for the detection of unfolded proteins, and to restore ER homeostasis via the UPR (reviewed by Hetz (2012)). The three sensors inositol-requiring protein 1 (Ire1), activating transcription factor 6 (ATF6), and PERK are membrane embedded proteins which synergistically re-establish ER homeostasis. For example, they induce chaperone synthesis (Yamamoto et al., 2007; Yoshida et al., 1998) to raise protein folding capacity, and they inhibit translation (Harding et al., 1999; Prostko et al., 1993) to relieve protein overload. In addition, autophagy (see below) emerges as the major mechanism for the clearance of misfolded proteins in the ER (Ding et al., 2007; Ogata et al., 2006), as ER stress suppresses proteasome mediated degradation (Menendez-Benito et al., 2005; Nijholt et al., 2011). If cells are unable to restore homeostasis, persistent ER stress leads to apoptosis, which needs to be circumvented by cancer cells.

The regulatory interaction between mTORC1 and ER stress can be understood as a bidirectional cross talk (reviewed by Appenzeller-Herzog and Hall (2012)) (**Fig. 1**). Mutations or knock outs of the TSC1 and TSC2 genes, leading to mTORC1 hyperactivation, sensitize cells to ER stress and apoptosis. This depends on mTORC1 as it can be reversed by raptor inhibition (Kang et al., 2011; Ozcan et al., 2008), further supporting that TSC1-TSC2 and mTORC1 jointly modulate ER stress. Conversely, ER stress may also modulate the activity of mTORC1 via the TSC1-TSC2 complex. In neuronal cells, short time periods of ER stress result in TSC1-TSC2 inactivation and subsequent mTORC1 activation, whereas prolonged stress activates the TSC1-TSC2 complex (Di Nardo et al., 2009). Whether this also occurs in cells other than neurons remains to be explored. Akt is another important mediator of ER stress dependent mTORC1 regulation: ER stress induces translation of activating transcription factor 4 (ATF4) which induces apoptosis by transcriptional activation of stress related proteins, including tribbles homolog 3 (TRB3) (Ohoka et al., 2005) which inhibits Akt. In addition, ER stress inhibits mTORC2 and its substrate Akt in a glycogen synthase kinase (GSK) 3-beta dependent manner (Chen et al., 2011). Furthermore, activation of mTORC1 by ER stress inhibits Akt via the NFLs, followed by activation of the Ire1- c-Jun NH(2)-terminal kinase (JNK) pathway, which in turn induces apoptosis (Kato et al., 2012). This suggests that cancer cells under chronic ER stress need to cope with Akt inactivation by multiple mechanisms (Chen et al., 2011; Kato et al., 2012; Ohoka et al., 2005). As active mTORC1 (Di Nardo et

al., 2009) contributes to Akt inhibition and apoptosis susceptibility (Di Nardo et al., 2009; Kang et al., 2011; Kato et al., 2012; Ozcan et al., 2008), cancer cells need to prevent mTORC1 hyperactivation, to maintain Akt sufficiently active and ensure their survival under ER stress.

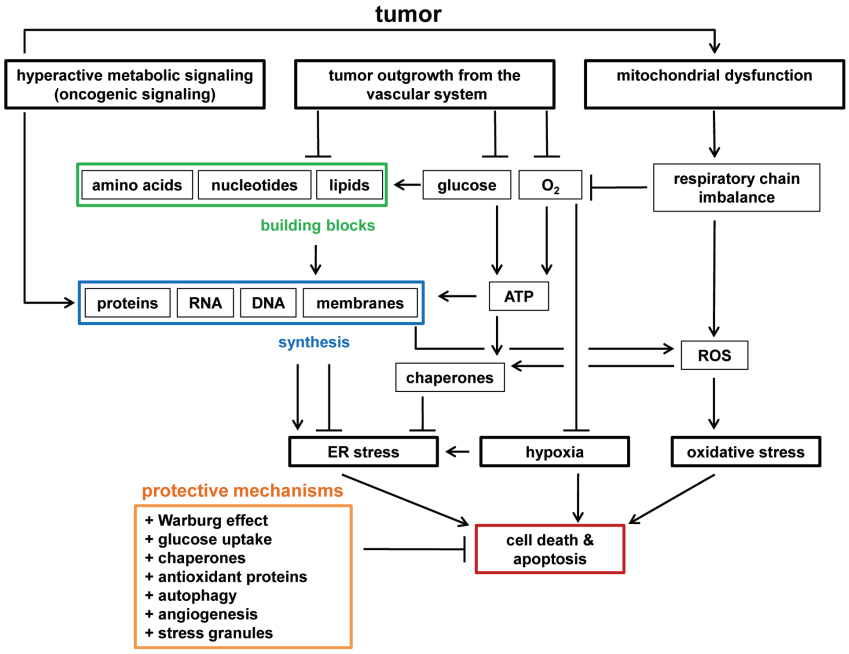

Figure 2. Stresses in tumors. Hyperactive metabolic signaling, e.g. induced by oncogenes, can result in increased synthesis of proteins, RNA, DNA, and membranes. Lipid synthesis is required for ER homeostasis, whereas hyperactive protein synthesis can induce ER stress. Tumors eventually outgrow the vascular system, leading to a shortage in glucose, oxygen and building blocks (amino acids, nucleotides, lipids). Glucose is required for ATP synthesis and is a carbon source for building block synthesis. Lack of ATP and building blocks inhibits lipid biosynthesis and chaperone activity. Therefore, ATP depletion enhances ER stress. Oxygen is required for ATP synthesis, and oxygen depletion results in hypoxia. ROS induce oxidative stress and originate from dysfunctions in mitochondria, e.g triggered by oncogenic signaling and mtDNA damage, respiratory chain imbalances, and lipid and protein biosynthesis. ER stress, hypoxia, and oxidative stress induce stress responses to restore cellular homeostasis, and eventually trigger apoptosis. Cancer cells have protective mechanisms to prevent apoptosis induced by chronic stresses. Examples are metabolic transformation (Warburg effect), glucose uptake, chaperone and antioxidant protein synthesis, autophagy, angiogenesis, and SG formation.

2.2. mTORC1 under hypoxia

The outgrowth of the tumor from the vascular system entails not only a shortage in glucose supply but also in oxygen (**Fig. 2**). This phenomenon is termed “hypoxia” and induces a stress response which can be monitored by the upregulation of the hypoxia inducible factors (HIFs) (Wilson and Hay, 2011). Oxygen shortage restricts the cellular capacity for ATP production as the respiratory chain requires aerobic conditions. Consequently, pyruvate is not entirely consumed by the TCA cycle but is – at least partially - converted into lactate to maintain the cellular redox balance (Wilson and Hay, 2011).

The hypoxia stress response adapts cells to low levels of oxidative respiration. Thus, hypoxia reduces energy consumption, activates glycolysis, and improves oxygen supply (reviewed by Majmundar et al. (2010)). The HIF transcription factors are key to the hypoxia induced stress response. HIF-1alpha induces gene products such as the vascular endothelial growth factors (VEGF) (Forsythe et al., 1996) which activate the growth of the vascular network (angiogenesis) (Choi et al., 2003) to restore oxygen availability. In addition, HIFs induce glycolysis and autophagy (see below). Of note, in cancer cells HIF upregulation often occurs without hypoxic conditions and thereby contributes to the Warburg effect (see below). Here, HIFs can be induced by oncogenic signaling via mTORC1 (Dodd et al., 2014; Sakamoto et al., 2014) and promote cell growth, proliferation, and survival. In addition to the HIFs, histone modifications have been reported to contribute to HIF independent transcriptional regulation under hypoxia (Johnson et al., 2008), but the underlying mechanisms and their potential interaction with mTOR signaling remain to be explored.

Hypoxia inactivates mTORC1 by different mechanisms (**Fig. 1**). Firstly, hypoxia increases the AMP:ATP ratio which activates AMPK (Gowans and Hardie, 2014; Hardie et al., 2012). Secondly, hypoxia activates the DNA damage response protein Ataxia telangiectasia mutated (ATM) in the cytosol, in a DNA damage independent manner (Cam et al., 2010). ATM phosphorylates HIF1alpha resulting in REDD1 (regulated in development and DNA damage responses 1) induction (Cam et al., 2010). REDD1 and mTORC1 are connected via a NFL: REDD1 inhibits mTORC1 via TSC1-TSC2 activation (Brugarolas et al., 2004; DeYoung et al., 2008; Sofer et al., 2005), whereas mTORC1 is necessary to stabilize the REDD1 protein (Kimball et al., 2008/2/8; Tan and Hagen, 2013). Furthermore, mTORC1 activity is also required for HIF1alpha expression (Dodd et al., 2014; Toschi et al., 2008). Thus, hypoxic cells require mTORC1

to re-establish homeostasis by the HIF1alpha and REDD1 dependent stress response. On the other hand, mTORC1 needs to be restricted, as otherwise the mTORC1-dependent NFLs inhibit Akt, leading to apoptosis sensitization. This is particularly relevant under hypoxia as Akt may be further inhibited by ATF4 induction (Tagliavacca et al., 2012). Thus, also under hypoxia inhibitory and stimulatory inputs contribute to net mTORC1 activity.

2.3. mTORC1 under oxidative stress

A third challenge commonly monitored in cancer cells is oxidative stress (**Fig. 2**). Oxidative stress is induced by the accumulation of reactive oxygen species (ROS). To comply with their high proliferation rate, cancer cells exhibit an accelerated metabolism which entails an increased activity of the respiratory chain and mitochondrial biogenesis (Sosa et al., 2013). This not only raises ATP production but may also increase cellular ROS (Sosa et al., 2013) due to temporary imbalances between reduction and oxidation at the level of the Complexes I and III of the respiratory chain (Desler et al., 2011). Also dysfunction of mitochondria in cancer cells (Woo et al., 2012) may contribute to increased ROS levels. Mutations in cancer cells tend to accumulate in mitochondrial DNA (mtDNA) (He et al., 2010; Yakes and Van Houten, 1997) and are enriched in genes coding for subunits of Complex I, III, and IV of the electron transport chain (Larman et al., 2012), which may eventually lead to ROS release. This also occurs during therapeutic intervention, as chemotherapies preferentially induce mutations in mtDNA, correlating with increased ROS formation (Carew et al., 2003; Chiara et al., 2012). Of note, ROS formation in cancer cells has been often linked with an induction of oncogenic signaling (Trachootham et al., 2009), for example of the mitogen activated protein kinase (MAPK) and PTEN/Akt pathways (Goo et al., 2012; Kodama et al., 2013; Vafa et al., 2002; Weyemi et al., 2012). For example, H-Ras activates the ROS-producing NADPH oxidase (NOX) (Irani et al., 1997) enzymes and suppresses the antioxidant molecule Sestrin 1 (Kopnin et al., 2007). Akt, in a 4E BP1-dependent manner, increases the activity of several respiratory complexes (Goo et al., 2012) and thus the potential of ROS formation, but the underlying mechanism remains elusive. Hence, multiple processes contribute to ROS formation in cancer cells.

How do cancer cells cope with these increased ROS levels? The response to oxidative stress is partially induced by ROS themselves. ROS can oxidize cysteines, leading to disulfide bond formation in proteins, thereby altering

their activity (reviewed by Groitl and Jakob (2014)). Via this mechanism, ROS activate chaperones to refold damaged proteins. One prominent example is the 2-Cys peroxiredoxin PrxII whose chaperone activity is induced by cysteine oxidation under oxidative stress (Moon et al., 2005). In addition, oxidative stress induces the key stress transcription factor Nuclear factor erythroid 2-like 2 (Nrf2) which controls the expression of several hundred genes comprising chaperones, antioxidant enzymes, or proteins of the inflammatory and immune response (reviewed by Sosa et al. (2013)). For example, cancer cells show upregulation of the anti-oxidative proteins glutathione, superoxide dismutase, catalase, and thioredoxin (reviewed by Watson (2013)) which is at least in part due to Nrf2-induced oncogenic signaling (reviewed by DeNicola et al. (2011)).

Early evidence for a complex mTORC1 regulation by ROS came from UV irradiation experiments. UV radiation activates mTORC1 during the first seven hours, with a decrease over time (Brenneisen et al., 2000; Huang et al., 2002; Parrott and Templeton, 1999), and mTORC1 activation can be prevented by hydrogen peroxide scavengers (Huang et al., 2002). Also chemical treatments with hydrogen peroxide or sodium arsenite affect mTORC1 in a dosage and time dependent manner (Wang and Proud, 1997). Generally speaking, short treatments and low concentrations seem to induce mTORC1, whereas prolonged treatments and high concentrations diminish or abolish mTORC1 activity (Bae et al., 1999; Thedieck et al., 2013; Zhang et al., 2013; Zheng et al., 2011). It should be noted though that dosage and time dependent effects of ROS on mTORC1 are highly context and cell type dependent. The tumor suppressor PTEN (Chetram et al., 2011; Denu and Tanner, 1998; Leslie et al., 2003) is redox sensitive and directly inactivated by cysteine oxidation, and also TSC1-TSC2 has been suggested to be directly oxidized by ROS (Yoshida et al., 2011) (**Fig. 1**). Thus, in cancer cells, ROS possibly contribute to chronic TSC1-TSC2 and PTEN inactivation and mTORC1-dependent metabolic induction. In contrast, Zhang et al. (2013) reported recently that mTORC1 can also be inactivated by ROS, and this depends on peroxisomal localization of TSC2. Furthermore, ROS activates cytoplasmic ATM (Alexander et al., 2010; Guo et al., 2010) and AMPK which both inhibit mTORC1 (reviewed by Hardie et al. (2012)). Thus, ROS have activating and inhibitory effects on mTORC1 whose net regulation (i.e. activation or inhibition) depends on the cellular context, persistence, and strength of the ROS stress.

2.4. Regulation of mTORC2 by stresses

Comparably little is known about the response of mTORC2 to stress, and we therefore focus in this review mostly on mTORC1. It should be noted though that increasing evidence additionally suggests mTORC2 as an important component of stress signaling. There are activating as well as inhibiting inputs on the mTORC2 network during different stresses. Examples are the inhibition of mTORC2 by ER stress (Chen et al., 2011) and oxidative stress (Muders et al., 2009; Wang et al., 2011) as well as the activation of mTORC2 during hypoxia (Li et al., 2007). ER stress results in GSK3beta dependent phosphorylation of rictor, which decreases the affinity of mTORC2 to its substrates (Chen et al., 2011), and oxidative stress leads to mTORC2 disruption and inactivation (Muders et al., 2009; Wang et al., 2011). The mechanism activating mTORC2 during hypoxia is not understood. mTORC2 activation during hypoxia is needed for the hypoxia stress response, as mTORC2 induces transcription of HIF1alpha and HIF2alpha (Toschi et al., 2008), and positively modulates hypoxia induced proliferation (Li et al., 2007).

2.5. Interconnection of ER stress, hypoxia and oxidative stress

Oxidative stress, hypoxia, and ER stress are closely intertwined and cannot be viewed separately. For example, lack of oxygen inhibits ATP production by the respiratory chain (Cantor and Sabatini, 2012), which at least in the short term mitigates chaperone mediated protein folding and thus induces ER stress. In addition, oxygen is the preferred terminal electron acceptor needed for disulphide bond formation (oxidative protein folding) within the ER (Koritzinsky et al., 2013; Tu and Weissman, 2002). Thus, hypoxia is able to induce ER stress (Rouschop et al., 2013; Rouschop et al., 2010). Conversely, severe ER stress induces oxidative protein folding (Marciniak et al., 2004) leading to ROS formation, which in a vicious cycle can lead to protein damage and reinforce again ER stress (Malhotra and Kaufman, 2007). Furthermore, glucose starvation (Blackburn et al., 1999; Spitz et al., 2000) as well as hypoxia (Chandel et al., 1998; Chandel et al., 2000) can induce ROS formation in tumor cells, but the underlying mechanisms are poorly understood. In conclusion, cancer cell traits are prone to induce stress at different levels; as oxidative stress, hypoxia, and ER stress can induce each other, they often occur in conjunction and cancer cells have to cope with chronic stress conditions which are prone to induce apoptosis (Carmeliet et al., 1998;

Hiramatsu et al., 2014; Kim et al., 2004; Li et al., 2010; Lu et al., 2014; Win et al., 2014). Yet, cancer cells acquire properties enabling them to escape programmed cell death (Delbridge et al., 2012; Singhapol et al., 2013; Thedieck et al., 2013) (see below).

3. Regulation of glucose and protein homeostasis by mTORC1 during stress

Hyperactive biosynthesis in proliferating cells causes a high demand for ATP and building blocks, but oxidative phosphorylation is also a source of cellular ROS, as discussed earlier. How do cancer cells cope with this challenge? During glycolysis one glucose molecule is converted into two ATP molecules and pyruvate. Pyruvate, under normoxic conditions, is introduced into the TCA cycle which via aerobic respiration theoretically generates 36 ATP molecules. However, under hypoxic conditions pyruvate is converted by lactate dehydrogenase (LDH) to lactate in the cytosol, without further generation of ATP. Cancer cells “ferment” glucose into lactate even under normoxic conditions (aerobic glycolysis) (Warburg, 1956). Although the ATP yield is low, aerobic conversion of glucose to lactate is fast, generates less ROS, and delivers carbon backbones for building block synthesis (reviewed by Hsu and Sabatini (2008)). This metabolic transformation, discovered by Otto Warburg nearly 100 years ago, is named “Warburg effect” (Warburg, 1956). Another shift of glucose metabolism in cancer cells is the induction of the PPP (reviewed by Sosa et al. (2013)). Diverting carbon from glycolysis into the PPP supplies increased levels of (1) R5P for nucleotide synthesis, needed for DNA replication and transcription (reviewed by Deberardinis et al. (2008)); and (2) NADPH, which supplies electrons for biosynthesis and eliminates ROS, thereby providing protection from oxidative stress. Glucose diversion into the PPP and into lactate is modulated by several mTOR network components that positively regulate glucose uptake and glycolysis: Akt promotes glucose uptake e.g. by stimulating the translocation of the glucose transporter 4 (GLUT4) (Garrido et al., 2013; Kohn et al., 1996) to the plasma membrane. Furthermore, AMPK inactivation is tumorigenic as AMPK inhibits the Warburg effect in a HIF1alpha dependent manner (Faubert et al., 2013). This may in fact be mediated by mTORC1, which is activated upon AMPK inhibition. mTORC1 induces HIF1alpha levels (Dodd et al., 2014; Sakamoto et al., 2014) which in turn can activate the expression of almost all glycolytic enzymes (Semenza, 2010).

mTORC1 and stresses also impinge on autophagy, a cell autonomous

process that maintains protein homeostasis (**Fig. 3**). During autophagy proteins and cell organelles are targeted to the lysosomes for degradation. In cancer cells, autophagy has an ambiguous function. On the one hand, autophagy has been suggested to prevent tumorigenesis, but in established tumors autophagy seems to promote stress survival (reviewed by Yang et al. (2011)). There are three different types of autophagy (reviewed in Boya et al. (2013) and Marino et al. (2014)); macroautophagy, microautophagy, and chaperon mediated autophagy. Macroautophagy, in the following termed autophagy, is divided into

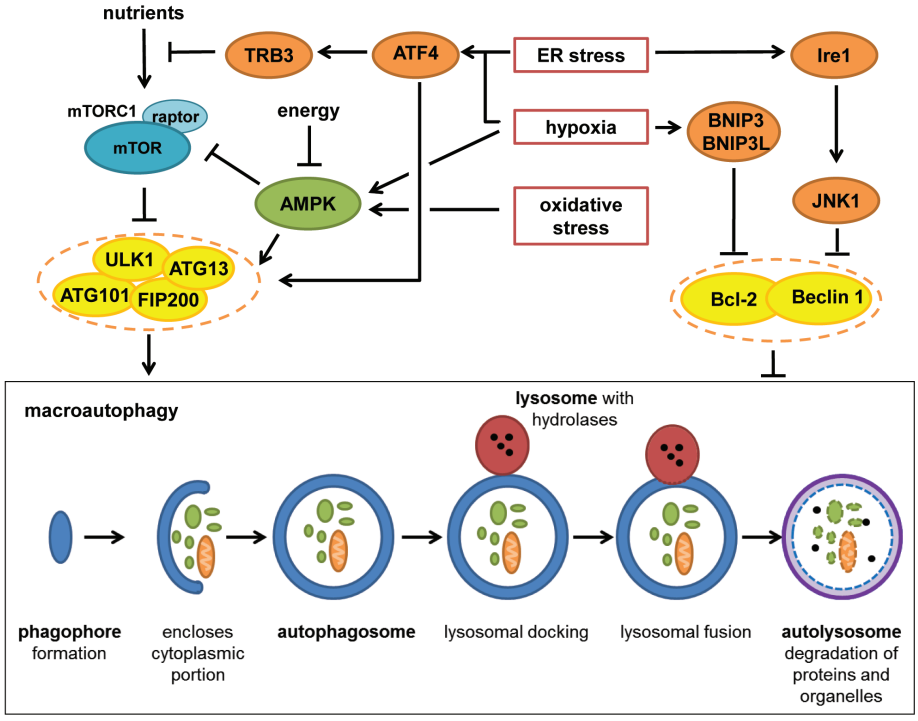

Figure 3. Autophagy regulation by stress. The ULK1 complex (ULK1, ATG13, ATG101 and FIP200) and the Bcl-2-Beclin 1 complex are main autophagy regulators. Autophagy can be divided in different steps: (1) phagophore formation and enlargement (autophagosome). (2) Lysosomal docking and fusion with the autophagosome (autolysosome). (3) Degradation of proteins and organelles in the autolysosome. The ULK1 complex is needed for autophagy initiation, whereas Bcl-2-Beclin 1 complex assembly prevents Beclin 1 from triggering autophagy. The ULK1 complex is inhibited by mTORC1 and activated by AMPK. AMPK also directly inhibits mTORC1. ER stress induces ATF4 which controls stress factor transcription, e.g. of TRB3, which is a negative effector upstream of mTORC1 (Akt inhibition). In addition, ATF4 has a positive effect on the ULK1 complex. ER stress activates Ire1 kinase which induces JNK1, leading to Bcl-2-Beclin 1 complex disassembly. Hypoxia also induces ATF4 expression, and activates AMPK. In addition, hypoxia induces autophagy by BNIP3/BNIP3L dependent disassembly of the Bcl-2-Beclin 1 complex. Oxidative stress induces autophagy in an AMPK dependent manner.

tightly regulated steps. First, a phagophore emulates and elongates to surround a cytoplasmic fraction. The resulting autophagosome docks and fuses with hydrolase-containing lysosomes enabling digestion of proteins and organelles. The resulting autolysosome consists of the inner membrane of the previous autophagosome and enables digestion of the proteins and organelles within the surrounded cytoplasmic fraction. The building blocks that are released by this process can be reused by the cell. Autophagy initiation (emulation and elongation of the phagophore) is positively controlled by the Unc-51-like kinase 1 (ULK1) complex, comprising the proteins ULK1, autophagy regulated proteins 13 and 110 (ATG13, ATG110) as well as FAK family kinase-interacting protein of 200 kDa (FIP200) (Ganley et al., 2009; Mercer et al., 2009). mTORC1 and AMPK phosphorylate ULK1 on different sites and thereby respectively inhibit or activate autophagy (Kim et al., 2011). mTORC1 phosphorylates ULK1 (Kim et al., 2011) and ATG13 (Ganley et al., 2009), reducing ULK1 complex stability and ULK1 kinase activity (Hosokawa et al., 2009; Jung et al., 2009). In contrast, AMPK binds to the mTORC1-bound ULK1 complex and phosphorylates raptor (Lee et al., 2010) and ULK1 (Kim et al., 2011), to activate autophagy. Another modulator of autophagy initiation is the Bcl 2/Beclin 1 complex which inhibits phagophore maturation (Pattingre et al., 2005). ER stress, hypoxia, and oxidative stress affect autophagy via mTORC1, AMPK, and Bcl 2/Beclin 1. The ER stress induced UPR results in Ire1 and JNK activation. JNK phosphorylates Bcl-2 (Pattingre et al., 2009; Wei et al., 2008), disrupting its binding to Beclin 1 and inducing autophagy. ER stress also induces autophagy when inhibiting the PI3K-Akt pathway (Kouroku et al., 2007) and mTORC1 (Qin et al., 2010). Both, ER stress and hypoxia induce ATF4 which directly upregulates ULK1 transcription and ULK1 complex activity (Pike et al., 2013; Rzymski et al., 2010). In addition, ATF4 induces TRB3 expression (Ohoka et al., 2005; Salazar et al., 2009) resulting in Akt inhibition, which may potentially induce autophagy via mTORC1 inhibition. Furthermore, hypoxia induces autophagy by activating AMPK (Papandreou et al., 2008) as well as BNIP3/BNIP3L (Azad et al., 2008; Bellot et al., 2009; Tracy et al., 2007), negative modulators of the Bcl-2/Beclin 1 complex. Little is known about autophagy regulation by oxidative stress. Oxidative stress induces AMPK, correlating with induction of autophagy (Huang et al., 2009). In addition, oxidative stress also activates chaperon mediated autophagy (Kiffin et al., 2004), a process in which proteins are unfolded and trans-localized directly through the lysosomal membrane.

In cancer cells, autophagy is necessary to maintain building block supply,

especially under starvation conditions. In addition, autophagy is able to counteract stresses like ER stress and oxidative stress by degrading damaged proteins and cell organelles. In keeping with this, the inactivation of the negative AMPK regulator FLCN leads to stress resistance via autophagy induction (Possik et al., 2014). Furthermore, autophagy inhibition correlates with induced apoptosis during cancer related hypoxia and thus seems to have an important function in tumor cell survival under endogenous stress (Degenhardt et al., 2006). In addition, autophagy induction often correlates with cancer resistance to chemotherapeutics (Ajabnoor et al., 2012; Amaral et al., 2012). In contrast, prolonged autophagy induction has been suggested to result in cell death (reviewed by Loos et al. (2013) and Marino et al. (2014)). Given that mTORC1 is a potent inhibitor of autophagy, it seems paradoxical that both mTORC1 and autophagy are required for cancer cell survival. This suggests that cancer cells need to maintain a delicate balance between mTORC1 activity and autophagy in order to benefit from both.

4. Balancing mTORC1 under stress: stress granules as guardians of cancer cells?

mTORC1 activity contributes in many aspects to cancer cell survival. However, chronic mTORC1 hyperactivation eventually inhibits autophagy and induces cell death, and therefore needs to be counterbalanced. Several inputs into the mTOR network, mainly impinging on TSC1-TSC2, Akt, and AMPK, restrict mTORC1 activity under stress, and thereby not only limit cellular growth, but also potentially enable autophagy and suppress cell death. SGs represent an additional buffer system in stressed cells. SGs form under a variety of stresses including hypoxia, ER, oxidative, heat, nutrient, osmotic, and cold stress (De Leeuw et al., 2007; Hofmann et al., 2012; Kedersha and Anderson, 2007). Protein synthesis is inhibited during stress, and polysome disassembly can be induced by many different stress sensors. The most prominent examples are eukaryotic translation initiation factor 2alpha (eIF2alpha) kinases (reviewed by Donnelly et al. (2013)), which phosphorylate eIF2alpha at serine 51. eIF2alpha is a subunit of eIF2 which forms together with t-RNAfMet and GTP the ternary complex, required for the formation of the 48S translation preinitiation complex. eIF2alpha phosphorylation prevents ternary complex formation leading to polysome disassembly and producing a non-canonical 48S* complex, unable to recruit the 60S ribosomal subunit. In mammals four eIF2alpha kinases are described: haemin-regulated

inhibitor (HRI), double-stranded RNA activated protein kinase (PKR), general control nonderepressible 2 (GCN2), and PERK. These kinases allow the cell to respond to a broad spectrum of stresses including oxidative stress (McEwen et al., 2005), ER stress (Harding et al., 2000) and amino acids starvation (Wek et al., 1995). Polysome disassembly changes the fate of many proteins involved in mRNA processing, to accumulate mRNAs that disassemble from polysomes. The morphological consequence of this process is the formation of cytoplasmic SGs which are protein-RNA assemblies(Anderson and Kedersha, 2002). SGs have an anti-apoptotic function under stress (Arimoto et al., 2008; Thedieck et al., 2013), and their formation after chemotherapy or radiotherapy in cancer correlates with therapy resistance (Fournier et al., 2013; Moeller et al., 2004). Thus, SGs could help the tumor to balance stress signaling and to prevent apoptosis under stresses elicited by the tumor environment or therapeutic interventions.

The first phases in SG aggregation or nucleation depend on SG nucleating proteins, which bind to the disrupted 48S*-mRNA complex. Overexpression of nucleators is often sufficient to induce SGs in vitro (Matsuki et al., 2013; Takahara and Maeda, 2012). Thus, overexpression of nucleators in vivo has the potential to promote SG formation in cancer cells. Examples for nucleators are Ras-GTPase activating protein SH-3 domain binding protein 1 and 2 (G3BP) (Matsuki et al., 2013; Tourriere et al., 2003), T cell intracellular antigen (TIA-1) and TIA-1-related protein (TIAR) (Kedersha et al., 2000; Kedersha et al., 1999), polyadenylate-binding protein 1 (PABP1) (Takahara and Maeda, 2012), and fragile X mental retardation protein (FMRP) (Didiot et al., 2009). Protein levels of SG nucleation factors are induced in several tumor entities (French et al., 2002; Guitard et al., 2001; Luca et al., 2013). For example, French et al. (2002) analyzed 22 breast cancer samples all of which showed elevated G3BP1. After the nucleation and aggregation phases, further proteins with intrinsic mRNA binding capacity, or which bind to SG proteins by piggy back recruitment, are assembled into SGs (Kedersha et al., 2013). Upon stress relief, SGs dissolve and SG proteins relocate to their previous compartments (Hofmann et al., 2012; Takahara and Maeda, 2012; Wippich et al., 2013). SGs are thought of as sites of RNA storage and triage during stress (Thomas et al., 2011). In addition, there is increasing evidence that SGs interfere with stress signaling pathways (reviewed by Kedersha et al. (2013)). Proteins involved in apoptosis can be recruited to SGs, which thereby promote survival. For example, SG recruitment of RACK1 (signaling scaffold protein receptor of activated protein kinase C 1) prevents apoptosis induction by the genotoxic stress-activated p38 and JNK MAPK

pathways (Arimoto et al., 2008); and ubiquitin-specific protease 10 (USP10) has been reported to exert an antioxidant apoptosis-preventing activity, which depends on USP10's recruitment to SGs (Takahashi et al., 2013). Recruitment of TNF receptor-associated factor 2 (TRAF2) to SGs inhibits proinflammatory tumor necrosis factor alpha (TNFalpha)-NF-kappaB signaling (Kim et al., 2005).

SG assembly in both yeast and human cells can inhibit TORC1/mTORC1 signaling (**Fig. 4**) by sequestering mTOR complex components, or the mTORC1 upstream modulator dual specificity tyrosine-phosphorylation-regulated kinase 3 (DYRK3) (Takahara and Maeda, 2012; Thedieck et al., 2013; Wippich et al., 2013). In cancer cells, DYRK3 integrates mTORC1 activity with SG formation via a dual mechanism (Wippich et al., 2013). During prolonged stress, DYRK3 is sequestered into SGs where it prevents SG dissolution and mTORC1 release from SGs. After stress release, DYRK3 phosphorylates and inhibits the mTORC1-inhibitor PRAS40 (Fonseca et al., 2007; Nascimento et al., 2010; Oshiro et al., 2007; Sancak et al., 2007; Thedieck et al., 2007; Vander Haar et al., 2007; Wang et al., 2008), thus contributing to mTORC1 reactivation. Furthermore, the adaptor protein astrin disassembles mTORC1 by sequestering raptor into SGs (Thedieck et al., 2013). By this recruitment, SGs restrict mTORC1 assembly and prevent its hyperactivation, and mTORC1-dependent oxidative stress induced apoptosis. Thus, astrin inhibition induces mTORC1-triggered apoptosis in cancer cells (Thedieck et al., 2013). Like other SG proteins, astrin is frequently overexpressed in tumors, and has been correlated with an unfavorable prognosis in human breast cancers and non-small-cell lung (NSCL) cancers (Buechler, 2009; Valk et al., 2010). This suggests that high astrin levels render cancer cells apoptosis-resistant by counteracting mTORC1 hyperactivation. Also in yeast, SG induction by heat shock or PABP1 overexpression leads to TOR inhibition by sequestration into SGs, and TORC1 re-activation after stress correlates with its release from SGs (Takahara and Maeda, 2012). Thus, SG formation has a conserved inhibitory effect on TORC1/mTORC1 in eukaryotic cells. However, mTORC1 activity is also needed for SG formation in mammalian cells (Fournier et al., 2013), for example, formation of 5'cap-eIF4F complexes requires 4EBP1-phosphorylation by mTORC1 (Heesom and Denton, 1999). Thus, SGs and mTORC1 are connected via a NFL, in which mTORC1 positively regulates SGs, whereas SGs inhibit mTORC1 (**Fig. 4**).

mTORC1 and SGs have both been linked to the regulation of translation and autophagy and it is interesting to consider how they may interact to control protein synthesis and autophagy under stress. During stress, 5'cap-dependent

translation is reduced, and this is linked to mTORC1 inhibition. For example, the SG components TIA-1 and TIAR inhibit translation of 5'TOP mRNAs, by promoting their assembly into SGs when mTORC1 is inhibited (Damgaard and Lykke-Andersen, 2011). However, in a background of mTORC1 inhibition and reduced overall translation, stress response proteins still need to be expressed (Yamasaki and Anderson, 2008), however, active translation requires mTORC1 activity. Thus, there is a seemingly contradictory requirement for mTORC1-activation/ inhibition during stress. SGs have emerged as an excellent candidate

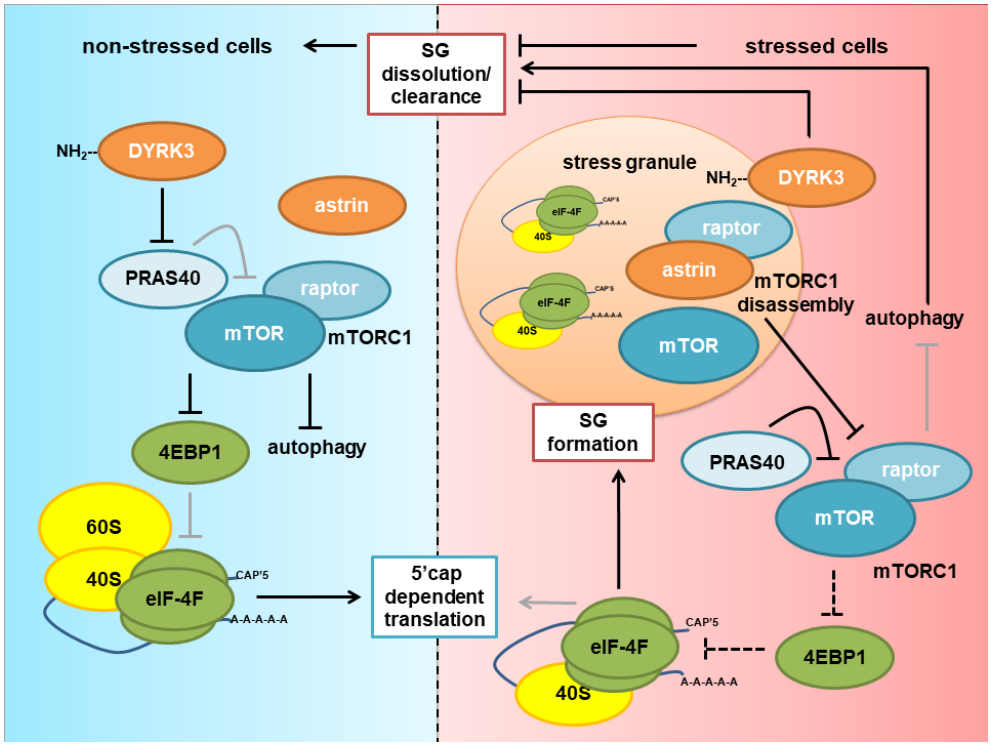

Figure 4. Stress granules and mTORC1. Under non-stressed conditions DYRK3 phosphorylates and inactivates the mTORC1 inhibitor PRAS40. Active mTORC1 inhibits 4E BP1, allowing for eIF4F-5'cap-mRNA complex formation, ribosomal binding, and translation initiation. Stressed conditions induce translational arrest, polysome disassembly, and SG formation. mTORC1 is disassembled, and the mTORC1 components mTOR and raptor are recruited to SGs. Kinase-inactive DYRK3 localizes to SGs by its N-terminus where it promotes SG stability and prevents mTOR release. Astrin binds to raptor and recruits it to SGs, thereby mediating SG-dependent mTORC1 disassembly. mTORC1 inactivation results in induced autophagy, which is required for SG clearance after stress release and for SG formation. However, 4E-BP1 inhibition by mTORC1 is required for SG formation, as 5'cap-eIF4F complexes and binding of the 40S ribosomal subunit are required for SG formation. Thus, SGs restrict mTORC1 activity, but some mTORC1 activity is needed for SG assembly (indicated by dashed arrows). Black arrows represent active connections, grey arrows represent inactive connections in stressed versus non-stressed cells.

for balancing mTORC1 activity and the dependent translational events. Both mTORC1 and SGs control translation of stress related factors (Chou et al., 2012; Hsieh et al., 2012; Huo et al., 2012; Iadevaia et al., 2012b; Thoreen et al., 2012), and SGs have been suggested as sites of stress-specific translation initiation (Buchan and Parker, 2009). Translation under stress depends on upstream open reading frames (uORFs) and internal ribosomal entry sites (IRES) (Holcik and Sonenberg, 2005; Holcik et al., 2000; Thomas et al., 2011; Vattem and Wek, 2004). mTORC1 induces both IRES-mediated (Dai et al., 2011; Grzmil and Hemmings, 2012) and uORF-dependent translation, via eIF4GI (Ramirez-Valle et al., 2008), a member of the eIF4F complex. For example, the stress related proteins heat shock factor protein 1 (HSF1), heterogeneous nuclear ribonucleoprotein A1 (hnRNP-A1), and 70 kilodalton heat shock protein (Hsp70) require mTORC1 for their expression under oxidative stress (Thedieck et al., 2013). hnRNP-A1 is required for IRES-mediated translation under stress in tumor cells(Damiano et al., 2012; Rubsamen et al., 2012), whereas HSF1 mediates transcriptional events under stress, including Hsp70 expression (Chou et al., 2012). Additionally, ATF4 protein expression under stress is mTORC1-regulated (Thedieck et al., 2013). The ATF4 mRNA contains two uORFs, leading to increased ATF4 translation in response to stress-related eIF2alpha phosphorylation (Vattem and Wek, 2004). ATF4 induces autophagy under ER stress and hypoxia (see above). Of note, autophagy is required for SG clearance in yeast and mammalian cells (Buchan et al., 2013; Seguin et al., 2014). Inhibition of autophagy results in mis-targeting of proteins to SGs (Seguin et al., 2014). Thus, it seems that while mTORC1 needs to be active to enable expression of stress factors, mTORC1 activity needs to be restricted to enable autophagy. mTORC1 and autophagy-mediated SG turnover may therefore represent a mechanism of feedback regulation balancing mTORC1 activity under stress.

5. Therapeutic implications: mTORC1 in stress as a target in cancer?

mTORC1 signaling is mostly perceived as a pro-survival and anti-apoptotic process. However, there is ample evidence that dysregulated hyperactive signaling via mTORC1, e.g. in response to TSC1-TSC2 inactivation, is prone to elicit cell death. How do cancer cells survive the inactivation of major negative regulators (i.e. tumor suppressors) of mTORC1 signaling in conjunction with a hyperactive metabolism and high stress levels? Persistent stresses eventually

trigger apoptosis in healthy cells. However, short term stresses and their consequences need to be buffered to prevent cell death induction by transient imbalances in cellular signaling, metabolism, and redox homeostasis. Therefore, signaling, transcription, translation, and metabolic networks are stabilized by multiple feedback loops and buffer systems. SGs represent one such buffer system. It is likely that cancer cells hijack this system by overexpressing SG components. This may render the tumor cells resistant to hyperactive signaling induced by oncogenic mutations, hyperactive metabolism and stresses, as well as therapeutic interventions such as chemotherapy (genotoxic stress) or irradiation. Signaling and metabolic networks that are hyperactive in cancer, such as mTORC1 signaling or glycolysis, often represent vital cellular functions that cannot be therapeutically targeted without major side effects on healthy tissues. SGs by contrast are likely to be more essential for cancer cells than for healthy tissues to overcome a stressed cellular environment. Thus, SG modulation represents a promising orthogonal approach to complement existing therapies involving targeted drugs or chemotherapeutics.

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References

Ajabnoor, G.M., Crook, T., and Coley, H.M. (2012). Paclitaxel resistance is associated with switch from apoptotic to autophagic cell death in MCF-7 breast cancer cells. Cell death & disease 3, e260.

Alexander, A., Cai, S.L., Kim, J., Nanez, A., Sahin, M., MacLean, K.H., Inoki, K., Guan, K.L., Shen, J., Person, M.D., et al. (2010). ATM signals to TSC2 in the cytoplasm to regulate mTORC1 in response to ROS. Proceedings of the National Academy of Sciences of the United States of America 107, 4153-4158.

Amaral, C., Borges, M., Melo, S., da Silva, E.T., Correia-da-Silva, G., and Teixeira, N. (2012). Apoptosis and autophagy in breast cancer cells following exemestane treatment. PloS one 7, e42398.

Anderson, P., and Kedersha, N. (2002). Stressful initiations. J Cell Sci 115, 3227-3234.

Appenzeller-Herzog, C., and Hall, M.N. (2012). Bidirectional crosstalk between endoplasmic reticulum stress and mTOR signaling. Trends in cell biology 22, 274-282.

Arimoto, K., Fukuda, H., Imajoh-Ohmi, S., Saito, H., and Takekawa, M. (2008). Formation of stress granules inhibits apoptosis by suppressing stress-responsive MAPK pathways. Nat Cell Biol 10, 1324-1332.

Azad, M.B., Chen, Y., Henson, E.S., Cizeau, J., McMillan-Ward, E., Israels, S.J., and Gibson, S.B. (2008). Hypoxia induces autophagic cell death in apoptosis-competent cells through a mechanism involving BNIP3. Autophagy 4, 195-204.

Bae, G.U., Seo, D.W., Kwon, H.K., Lee, H.Y., Hong, S., Lee, Z.W., Ha, K.S., Lee, H.W., and Han, J.W. (1999). Hydrogen peroxide activates p70(S6k) signaling pathway. The Journal of biological chemistry 274, 32596-32602.

Bar-Peled, L., and Sabatini, D.M. (2014). Regulation of mTORC1 by amino acids. Trends in cell biology 24, 400-406.

Bar-Peled, L., Schweitzer, L.D., Zoncu, R., and Sabatini, D.M. (2012). Ragulator is a GEF for the rag GTPases that signal amino acid levels to mTORC1. Cell 150, 1196-1208.

Bellot, G., Garcia-Medina, R., Gounon, P., Chiche, J., Roux, D., Pouyssegur, J., and Mazure, N.M. (2009). Hypoxia-induced autophagy is mediated through hypoxia-inducible factor induction of BNIP3 and BNIP3L via their BH3 domains. Molecular and cellular biology 29, 2570-2581.

Ben-Sahra, I., Howell, J.J., Asara, J.M., and Manning, B.D. (2013). Stimulation of de novo pyrimidine synthesis by growth signaling through mTOR and S6K1. Science 339, 1323-1328.

Blackburn, R.V., Spitz, D.R., Liu, X., Galoforo, S.S., Sim, J.E., Ridnour, L.A., Chen, J.C., Davis, B.H., Corry, P.M., and Lee, Y.J. (1999). Metabolic oxidative stress activates signal transduction and gene expression during glucose deprivation in human tumor cells. Free radical biology & medicine 26, 419-430.

Boya, P., Reggiori, F., and Codogno, P. (2013). Emerging regulation and functions of autophagy. Nat Cell Biol 15, 713-720.

Braakman, I., and Hebert, D.N. (2013). Protein folding in the endoplasmic reticulum. Cold Spring Harbor perspectives in biology 5, a013201.

Brahimi-Horn, M.C., Chiche, J., and Pouyssegur, J. (2007). Hypoxia and cancer. Journal of molecular medicine 85, 1301-1307.

Brenneisen, P., Wenk, J., Wlaschek, M., Krieg, T., and Scharffetter-Kochanek, K. (2000). Activation of p70 ribosomal protein S6 kinase is an essential step in the DNA damage-dependent signaling pathway responsible for the ultraviolet B-mediated increase in interstitial collagenase (MMP-1) and stromelysin-1 (MMP-3) protein levels in human dermal fibroblasts. The Journal of biological chemistry 275, 4336-4344.

Brugarolas, J., Lei, K., Hurley, R.L., Manning, B.D., Reiling, J.H., Hafen, E., Witters, L.A., Ellisen, L.W., and Kaelin, W.G., Jr. (2004). Regulation of mTOR function in response to hypoxia by REDD1 and the TSC1/TSC2 tumor suppressor complex. Genes & development 18, 2893-2904.

Brunet, A., Bonni, A., Zigmond, M.J., Lin, M.Z., Juo, P., Hu, L.S., Anderson, M.J., Arden, K.C., Blenis, J., and Greenberg, M.E. (1999). Akt promotes cell survival by phosphorylating and inhibiting a Forkhead transcription factor. Cell 96, 857-868.

Buchan, J.R., Kolaitis, R.M., Taylor, J.P., and Parker, R. (2013). Eukaryotic stress granules are cleared by autophagy and Cdc48/VCP function. Cell 153, 1461-1474.

Buchan, J.R., and Parker, R. (2009). Eukaryotic stress granules: the ins and outs of translation. Molecular cell 36, 932-941.

Buechler, S. (2009). Low expression of a few genes indicates good prognosis in estrogen receptor positive breast cancer. BMC cancer 9, 243.

Buller, C.L., Loberg, R.D., Fan, M.H., Zhu, Q., Park, J.L., Vesely, E., Inoki, K., Guan, K.L., and Brosius, F.C., 3rd (2008). A GSK-3/TSC2/mTOR pathway regulates glucose uptake and GLUT1 glucose transporter expression. American journal of physiology Cell physiology 295, C836-843.

Cam, H., Easton, J.B., High, A., and Houghton, P.J. (2010). mTORC1 signaling under hypoxic conditions is controlled by ATM-dependent phosphorylation of HIF-1alpha. Molecular cell 40, 509-520.

Cantor, J.R., and Sabatini, D.M. (2012). Cancer cell metabolism: one hallmark, many faces. Cancer discovery 2, 881-898.

Carew, J.S., Zhou, Y., Albitar, M., Carew, J.D., Keating, M.J., and Huang, P. (2003). Mitochondrial DNA mutations in primary leukemia cells after chemotherapy: clinical significance and therapeutic implications. Leukemia 17, 1437-1447.

Carmeliet, P., Dor, Y., Herbert, J.M., Fukumura, D., Brusselmans, K., Dewerchin, M., Neeman, M., Bono, F., Abramovitch, R., Maxwell, P., et al. (1998). Role of HIF-1alpha in hypoxia-mediated apoptosis, cell proliferation and tumour angiogenesis. Nature 394, 485-490.

Chandel, N.S., Maltepe, E., Goldwasser, E., Mathieu, C.E., Simon, M.C., and Schumacker, P.T. (1998). Mitochondrial reactive oxygen species trigger hypoxia-induced transcription. Proceedings of the National Academy of Sciences of the United States of America 95, 11715-11720.

Chandel, N.S., McClintock, D.S., Feliciano, C.E., Wood, T.M., Melendez, J.A., Rodriguez, A.M., and Schumacker, P.T. (2000). Reactive oxygen species generated at mitochondrial complex III stabilize hypoxia-inducible factor-1alpha during hypoxia: a mechanism of O2 sensing. The Journal of biological chemistry 275, 25130-25138.

Chauvin, C., Koka, V., Nouschi, A., Mieulet, V., Hoareau-Aveilla, C., Dreazen, A., Cagnard, N., Carpentier, W., Kiss, T., Meyuhas, O., et al. (2014). Ribosomal protein S6 kinase activity controls the ribosome biogenesis transcriptional program. Oncogene 33, 474-483.

Chen, C.H., Shaikenov, T., Peterson, T.R., Aimbetov, R., Bissenbaev, A.K., Lee, S.W., Wu, J., Lin, H.K., and Sarbassov dos, D. (2011). ER stress inhibits mTORC2 and Akt signaling

through GSK-3beta-mediated phosphorylation of rictor. Science signaling 4, ra10.

Chetram, M.A., Don-Salu-Hewage, A.S., and Hinton, C.V. (2011). ROS enhances CXCR4-mediated functions through inactivation of PTEN in prostate cancer cells. Biochem Biophys Res Commun 410, 195-200.

Chiara, F., Gambalunga, A., Sciacovelli, M., Nicolli, A., Ronconi, L., Fregona, D., Bernardi, P., Rasola, A., and Trevisan, A. (2012). Chemotherapeutic induction of mitochondrial oxidative stress activates GSK-3alpha/beta and Bax, leading to permeability transition pore opening and tumor cell death. Cell death & disease 3, e444.

Choi, K.S., Bae, M.K., Jeong, J.W., Moon, H.E., and Kim, K.W. (2003). Hypoxia-induced angiogenesis during carcinogenesis. Journal of biochemistry and molecular biology 36, 120-127.

Chou, S.D., Prince, T., Gong, J., and Calderwood, S.K. (2012). mTOR is essential for the proteotoxic stress response, HSF1 activation and heat shock protein synthesis. PloS one 7, e39679.

Chung, J., Kuo, C.J., Crabtree, G.R., and Blenis, J. (1992). Rapamycin-FKBP specifically blocks growth-dependent activation of and signaling by the 70 kd S6 protein kinases. Cell 69, 1227-1236.

Clarke, H.J., Chambers, J.E., Liniker, E., and Marciniak, S.J. (2014). Endoplasmic reticulum stress in malignancy. Cancer cell 25, 563-573.

Cornu, M., Albert, V., and Hall, M.N. (2013). mTOR in aging, metabolism, and cancer. Current opinion in genetics & development 23, 53-62.

Csibi, A., Fendt, S.M., Li, C., Poulogiannis, G., Choo, A.Y., Chapski, D.J., Jeong, S.M., Dempsey, J.M., Parkhitko, A., Morrison, T., et al. (2013). The mTORC1 pathway stimulates glutamine metabolism and cell proliferation by repressing SIRT4. Cell 153, 840-854.

Cunningham, J.T., Rodgers, J.T., Arlow, D.H., Vazquez, F., Mootha, V.K., and Puigserver, P. (2007). mTOR controls mitochondrial oxidative function through a YY1-PGC-1alpha transcriptional complex. Nature 450, 736-740.

Dai, N., Rapley, J., Angel, M., Yanik, M.F., Blower, M.D., and Avruch, J. (2011). mTOR phosphorylates IMP2 to promote IGF2 mRNA translation by internal ribosomal entry. Genes & development 25, 1159-1172.

Damgaard, C.K., and Lykke-Andersen, J. (2011). Translational coregulation of 5'TOP mRNAs by TIA-1 and TIAR. Genes & development 25, 2057-2068.

Damiano, F., Rochira, A., Tocci, R., Alemanno, S., Gnoni, A., and Siculella, L. (2012). HnRNP A1 mediates the activation of the IRES-dependent SREBP-1a mRNA translation in response to endoplasmic reticulum stress. The Biochemical journal.

De Leeuw, F., Zhang, T., Wauquier, C., Huez, G., Kruys, V., and Gueydan, C. (2007). The cold-inducible RNA-binding protein migrates from the nucleus to cytoplasmic stress granules by a methylation-dependent mechanism and acts as a translational repressor. Exp Cell Res 313, 4130-4144.

Deberardinis, R.J., Sayed, N., Ditsworth, D., and Thompson, C.B. (2008). Brick by brick: metabolism and tumor cell growth. Current opinion in genetics & development 18, 54-61.

Degenhardt, K., Mathew, R., Beaudoin, B., Bray, K., Anderson, D., Chen, G., Mukherjee, C., Shi, Y., Gelinas, C., Fan, Y., et al. (2006). Autophagy promotes tumor cell survival and restricts necrosis, inflammation, and tumorigenesis. Cancer cell 10, 51-64.

Delbridge, A.R., Valente, L.J., and Strasser, A. (2012). The role of the apoptotic machinery in tumor suppression. Cold Spring Harbor perspectives in biology 4.

Demetriades, C., Doumpas, N., and Teleman, A.A. (2014). Regulation of TORC1 in response to amino acid starvation via lysosomal recruitment of TSC2. Cell 156, 786-799.

DeNicola, G.M., Karreth, F.A., Humpton, T.J., Gopinathan, A., Wei, C., Frese, K., Mangal, D., Yu, K.H., Yeo, C.J., Calhoun, E.S., et al. (2011). Oncogene-induced Nrf2 transcription promotes ROS detoxification and tumorigenesis. Nature 475, 106-109.

Denu, J.M., and Tanner, K.G. (1998). Specific and reversible inactivation of protein tyrosine phosphatases by hydrogen peroxide: evidence for a sulfenic acid intermediate and implications for redox regulation. Biochemistry 37, 5633-5642.

Desler, C., Marcker, M.L., Singh, K.K., and Rasmussen, L.J. (2011). The importance of mitochondrial DNA in aging and cancer. J Aging Res 2011, 407536.

DeYoung, M.P., Horak, P., Sofer, A., Sgroi, D., and Ellisen, L.W. (2008). Hypoxia regulates TSC1/2-mTOR signaling and tumor suppression through REDD1-mediated 14-3-3 shuttling. Genes & development 22, 239-251.

Di Nardo, A., Kramvis, I., Cho, N., Sadowski, A., Meikle, L., Kwiatkowski, D.J., and Sahin, M. (2009). Tuberous sclerosis complex activity is required to control neuronal stress responses in an mTOR-dependent manner. The Journal of neuroscience : the official journal of the Society for Neuroscience 29, 5926-5937.

Didiot, M.C., Subramanian, M., Flatter, E., Mandel, J.L., and Moine, H. (2009). Cells lacking the fragile X mental retardation protein (FMRP) have normal RISC activity but exhibit altered stress granule assembly. Molecular biology of the cell 20, 428-437.

Ding, W.X., Ni, H.M., Gao, W., Yoshimori, T., Stolz, D.B., Ron, D., and Yin, X.M. (2007). Linking of autophagy to ubiquitin-proteasome system is important for the regulation of endoplasmic reticulum stress and cell viability. The American journal of pathology 171, 513-524.

Dodd, K.M., Yang, J., Shen, M.H., Sampson, J.R., and Tee, A.R. (2014). mTORC1 drives HIF-1alpha and VEGF-A signalling via multiple mechanisms involving 4E-BP1, S6K1 and STAT3. Oncogene.

Donnelly, N., Gorman, A.M., Gupta, S., and Samali, A. (2013). The eIF2alpha kinases: their structures and functions. Cellular and molecular life sciences : CMLS 70, 3493-3511.

Duran, R.V., Oppliger, W., Robitaille, A.M., Heiserich, L., Skendaj, R., Gottlieb, E., and Hall, M.N. (2012). Glutaminolysis activates Rag-mTORC1 signaling. Molecular cell 47, 349-358.

Duvel, K., Yecies, J.L., Menon, S., Raman, P., Lipovsky, A.I., Souza, A.L., Triantafellow, E., Ma, Q., Gorski, R., Cleaver, S., et al. (2010). Activation of a metabolic gene regulatory network downstream of mTOR complex 1. Molecular cell 39, 171-183.

Faubert, B., Boily, G., Izreig, S., Griss, T., Samborska, B., Dong, Z., Dupuy, F., Chambers, C., Fuerth, B.J., Viollet, B., et al. (2013). AMPK is a negative regulator of the Warburg effect and suppresses tumor growth in vivo. Cell Metab 17, 113-124.

Fels, D.R., and Koumenis, C. (2006). The PERK/eIF2alpha/ATF4 module of the UPR in hypoxia resistance and tumor growth. Cancer biology & therapy 5, 723-728.

Fonseca, B.D., Smith, E.M., Lee, V.H., MacKintosh, C., and Proud, C.G. (2007). PRAS40 is a target for mammalian target of rapamycin complex 1 and is required for signaling downstream of this complex. The Journal of biological chemistry 282, 24514-24524.

Forsythe, J.A., Jiang, B.H., Iyer, N.V., Agani, F., Leung, S.W., Koos, R.D., and Semenza, G.L. (1996). Activation of vascular endothelial growth factor gene transcription by hypoxia-inducible factor 1. Molecular and cellular biology 16, 4604-4613.

Fournier, M.J., Coudert, L., Mellaoui, S., Adjibade, P., Gareau, C., Cote, M.F., Sonenberg, N., Gaudreault, R.C., and Mazroui, R. (2013). Inactivation of the mTORC1-eukaryotic translation initiation factor 4E pathway alters stress granule formation. Molecular and cellular biology 33, 2285-2301.

French, J., Stirling, R., Walsh, M., and Kennedy, H.D. (2002). The expression of Ras-GTPase activating protein SH3 domain-binding proteins, G3BPs, in human breast cancers. The Histochemical journal 34, 223-231.

Ganley, I.G., Lam du, H., Wang, J., Ding, X., Chen, S., and Jiang, X. (2009). ULK1.ATG13.FIP200 complex mediates mTOR signaling and is essential for autophagy. The Journal of biological chemistry 284, 12297-12305.

Garrido, P., Moran, J., Alonso, A., Gonzalez, S., and Gonzalez, C. (2013). 17beta-estradiol activates glucose uptake via GLUT4 translocation and PI3K/Akt signaling pathway in MCF-7 cells. Endocrinology 154, 1979-1989.

Goo, C.K., Lim, H.Y., Ho, Q.S., Too, H.P., Clement, M.V., and Wong, K.P. (2012). PTEN/Akt signaling controls mitochondrial respiratory capacity through 4E-BP1. PloS one 7, e45806.

Gowans, G.J., and Hardie, D.G. (2014). AMPK: a cellular energy sensor primarily regulated by AMP. Biochemical Society transactions 42, 71-75.

Groitl, B., and Jakob, U. (2014). Thiol-based redox switches. Biochimica et biophysica acta 1844, 1335-1343.

Grzmil, M., and Hemmings, B.A. (2012). Translation regulation as a therapeutic target in cancer. Cancer research 72, 3891-3900.

Guitard, E., Parker, F., Millon, R., Abecassis, J., and Tocque, B. (2001). G3BP is overexpressed in human tumors and promotes S phase entry. Cancer letters 162, 213-221.

Guo, Z., Kozlov, S., Lavin, M.F., Person, M.D., and Paull, T.T. (2010). ATM activation by oxidative stress. Science 330, 517-521.

Gwinn, D.M., Shackelford, D.B., Egan, D.F., Mihaylova, M.M., Mery, A., Vasquez, D.S., Turk, B.E., and Shaw, R.J. (2008). AMPK phosphorylation of raptor mediates a metabolic checkpoint. Molecular cell 30, 214-226.

Hagiwara, A., Cornu, M., Cybulski, N., Polak, P., Betz, C., Trapani, F., Terracciano, L., Heim, M.H., Ruegg, M.A., and Hall, M.N. (2012). Hepatic mTORC2 Activates Glycolysis and Lipogenesis through Akt, Glucokinase, and SREBP1c. Cell Metab 15, 725-738.

Hara, K., Maruki, Y., Long, X., Yoshino, K., Oshiro, N., Hidayat, S., Tokunaga, C., Avruch, J., and Yonezawa, K. (2002). Raptor, a binding partner of target of rapamycin (TOR), mediates TOR action. Cell 110, 177-189.

Hardie, D.G., and Ashford, M.L. (2014). AMPK: regulating energy balance at the cellular and whole body levels. Physiology 29, 99-107.

Hardie, D.G., Ross, F.A., and Hawley, S.A. (2012). AMPK: a nutrient and energy sensor that maintains energy homeostasis. Nat Rev Mol Cell Biol 13, 251-262.

Harding, H.P., Zhang, Y., Bertolotti, A., Zeng, H., and Ron, D. (2000). Perk is essential for translational regulation and cell survival during the unfolded protein response. Molecular cell 5, 897-904.

Harding, H.P., Zhang, Y., and Ron, D. (1999). Protein translation and folding are coupled by an endoplasmic-reticulum-resident kinase. Nature 397, 271-274.

Harrington, L.S., Findlay, G.M., Gray, A., Tolkacheva, T., Wigfield, S., Rebholz, H., Barnett, J., Leslie, N.R., Cheng, S., Shepherd, P.R., et al. (2004). The TSC1-2 tumor suppressor controls insulin-PI3K signaling via regulation of IRS proteins. J Cell Biol 166, 213-223.

He, Y., Wu, J., Dressman, D.C., Iacobuzio-Donahue, C., Markowitz, S.D., Velculescu, V.E., Diaz, L.A., Jr., Kinzler, K.W., Vogelstein, B., and Papadopoulos, N. (2010). Heteroplasmic mitochondrial DNA mutations in normal and tumour cells. Nature 464, 610-614.

Heesom, K.J., and Denton, R.M. (1999). Dissociation of the eukaryotic initiation factor-4E/4E-BP1 complex involves phosphorylation of 4E-BP1 by an mTOR-associated kinase. FEBS letters 457, 489-493.

Hetz, C. (2012). The unfolded protein response: controlling cell fate decisions under ER stress and beyond. Nat Rev Mol Cell Biol 13, 89-102.

Hiramatsu, N., Messah, C., Han, J., LaVail, M.M., Kaufman, R.J., and Lin, J.H. (2014). Translational and posttranslational regulation of XIAP by eIF2alpha and ATF4 promotes ER stress-induced cell death during the unfolded protein response. Molecular biology of the cell 25, 1411-1420.

Hofmann, S., Cherkasova, V., Bankhead, P., Bukau, B., and Stoecklin, G. (2012). Translation suppression promotes stress granule formation and cell survival in response to cold shock. Molecular biology of the cell 23, 3786-3800.

Holcik, M., and Sonenberg, N. (2005). Translational control in stress and apoptosis. Nat Rev Mol Cell Biol 6, 318-327.

Holcik, M., Sonenberg, N., and Korneluk, R.G. (2000). Internal ribosome initiation of translation and the control of cell death. Trends Genet 16, 469-473.

Hosokawa, N., Hara, T., Kaizuka, T., Kishi, C., Takamura, A., Miura, Y., Iemura, S., Natsume, T., Takehana, K., Yamada, N., et al. (2009). Nutrient-dependent mTORC1 association with the ULK1-Atg13-FIP200 complex required for autophagy. Molecular biology of the cell 20, 1981-1991.

Hsieh, A.C., Liu, Y., Edlind, M.P., Ingolia, N.T., Janes, M.R., Sher, A., Shi, E.Y., Stumpf, C.R., Christensen, C., Bonham, M.J., et al. (2012). The translational landscape of mTOR signalling steers cancer initiation and metastasis. Nature 485, 55-61.

Hsu, P.P., Kang, S.A., Rameseder, J., Zhang, Y., Ottina, K.A., Lim, D., Peterson, T.R., Choi, Y., Gray, N.S., Yaffe, M.B., et al. (2011). The mTOR-regulated phosphoproteome reveals a mechanism of mTORC1-mediated inhibition of growth factor signaling. Science 332, 1317-1322.

Hsu, P.P., and Sabatini, D.M. (2008). Cancer cell metabolism: Warburg and beyond. Cell 134, 703-707.

Huang, C., Li, J., Ke, Q., Leonard, S.S., Jiang, B.H., Zhong, X.S., Costa, M., Castranova, V., and Shi, X. (2002). Ultraviolet-induced phosphorylation of p70(S6K) at Thr(389) and Thr(421)/Ser(424) involves hydrogen peroxide and mammalian target of rapamycin but not Akt and atypical protein kinase C. Cancer research 62, 5689-5697.

Huang, Q., Wu, Y.T., Tan, H.L., Ong, C.N., and Shen, H.M. (2009). A novel function of poly(ADP-ribose) polymerase-1 in modulation of autophagy and necrosis under oxidative stress. Cell Death Differ 16, 264-277.

Huo, Y., Iadevaia, V., Yao, Z., Kelly, I., Cosulich, S., Guichard, S., Foster, L.J., and Proud, C.G. (2012). Stable isotope-labelling analysis of the impact of inhibition of the mammalian target of rapamycin on protein synthesis. The Biochemical journal 444, 141-151.

Iadevaia, V., Huo, Y., Zhang, Z., Foster, L.J., and Proud, C.G. (2012a). Roles of the mammalian target of rapamycin, mTOR, in controlling ribosome biogenesis and protein synthesis. Biochemical Society transactions 40, 168-172.

Iadevaia, V., Wang, X., Yao, Z., Foster, L.J., and Proud, C.G. (2012b). Evaluation of mTOR-regulated mRNA translation. Methods Mol Biol 821, 171-185.

Iadevaia, V., Zhang, Z., Jan, E., and Proud, C.G. (2012c). mTOR signaling regulates the processing of pre-rRNA in human cells. Nucleic Acids Res 40, 2527-2539.

Inoki, K., Li, Y., Xu, T., and Guan, K.L. (2003a). Rheb GTPase is a direct target of TSC2 GAP activity and regulates mTOR signaling. Genes & development 17, 1829-1834.

Inoki, K., Zhu, T., and Guan, K.L. (2003b). TSC2 mediates cellular energy response to control cell growth and survival. Cell 115, 577-590.

Irani, K., Xia, Y., Zweier, J.L., Sollott, S.J., Der, C.J., Fearon, E.R., Sundaresan, M., Finkel, T., and Goldschmidt-Clermont, P.J. (1997). Mitogenic signaling mediated by oxidants in Ras-transformed fibroblasts. Science 275, 1649-1652.

Jeon, T.I., and Osborne, T.F. (2012). SREBPs: metabolic integrators in physiology and metabolism. Trends Endocrinol Metab 23, 65-72.

Johnson, A.B., Denko, N., and Barton, M.C. (2008). Hypoxia induces a novel signature of chromatin modifications and global repression of transcription. Mutation research 640, 174-179.

Jung, C.H., Jun, C.B., Ro, S.H., Kim, Y.M., Otto, N.M., Cao, J., Kundu, M., and Kim, D.H. (2009). ULK-Atg13-FIP200 complexes mediate mTOR signaling to the autophagy machinery. Molecular biology of the cell 20, 1992-2003.

Kang, Y.J., Lu, M.K., and Guan, K.L. (2011). The TSC1 and TSC2 tumor suppressors are required for proper ER stress response and protect cells from ER stress-induced apoptosis. Cell Death Differ 18, 133-144.

Kato, H., Nakajima, S., Saito, Y., Takahashi, S., Katoh, R., and Kitamura, M. (2012). mTORC1 serves ER stress-triggered apoptosis via selective activation of the IRE1-JNK pathway. Cell Death Differ 19, 310-320.

Kedersha, N., and Anderson, P. (2007). Mammalian stress granules and processing bodies. Methods in enzymology 431, 61-81.

Kedersha, N., Cho, M.R., Li, W., Yacono, P.W., Chen, S., Gilks, N., Golan, D.E., and Anderson, P. (2000). Dynamic shuttling of TIA-1 accompanies the recruitment of mRNA to mammalian stress granules. J Cell Biol 151, 1257-1268.

Kedersha, N., Ivanov, P., and Anderson, P. (2013). Stress granules and cell signaling: more than just a passing phase? Trends in biochemical sciences 38, 494-506.

Kedersha, N.L., Gupta, M., Li, W., Miller, I., and Anderson, P. (1999). RNA-binding proteins TIA-1 and TIAR link the phosphorylation of eIF-2 alpha to the assembly of mammalian stress granules. J Cell Biol 147, 1431-1442.

Kiffin, R., Christian, C., Knecht, E., and Cuervo, A.M. (2004). Activation of chaperone-mediated autophagy during oxidative stress. Molecular biology of the cell 15, 4829-4840.

Kim, D.H., Sarbassov, D.D., Ali, S.M., King, J.E., Latek, R.R., Erdjument-Bromage, H., Tempst, P., and Sabatini, D.M. (2002). mTOR interacts with raptor to form a nutrient-sensitive complex that signals to the cell growth machinery. Cell 110, 163-175.

Kim, E., Goraksha-Hicks, P., Li, L., Neufeld, T.P., and Guan, K.L. (2008). Regulation of TORC1 by Rag GTPases in nutrient response. Nat Cell Biol 10, 935-945.

Kim, J., Kundu, M., Viollet, B., and Guan, K.L. (2011). AMPK and mTOR regulate autophagy through direct phosphorylation of Ulk1. Nat Cell Biol 13, 132-141.

Kim, J.Y., Ahn, H.J., Ryu, J.H., Suk, K., and Park, J.H. (2004). BH3-only protein Noxa is a mediator of hypoxic cell death induced by hypoxia-inducible factor 1alpha. The Journal of experimental medicine 199, 113-124.

Kim, S.G., Hoffman, G.R., Poulogiannis, G., Buel, G.R., Jang, Y.J., Lee, K.W., Kim, B.Y., Erikson, R.L., Cantley, L.C., Choo, A.Y., et al. (2013). Metabolic stress controls mTORC1 lysosomal localization and dimerization by regulating the TTT-RUVBL1/2 complex. Molecular cell 49, 172-185.

Kim, W.J., Back, S.H., Kim, V., Ryu, I., and Jang, S.K. (2005). Sequestration of TRAF2 into stress granules interrupts tumor necrosis factor signaling under stress conditions. Molecular and cellular biology 25, 2450-2462.

Kimball, S.R., Do, A.N., Kutzler, L., Cavener, D.R., and Jefferson, L.S. (2008/2/8). Rapid Turnover of the mTOR Complex 1 (mTORC1) Repressor REDD1 and Activation of mTORC1 Signaling following Inhibition of Protein Synthesis. JBiolChem 283, 3465-3475.

Kodama, R., Kato, M., Furuta, S., Ueno, S., Zhang, Y., Matsuno, K., Yabe-Nishimura, C., Tanaka, E., and Kamata, T. (2013). ROS-generating oxidases Nox1 and Nox4 contribute to oncogenic Ras-induced premature senescence. Genes to cells : devoted to molecular & cellular mechanisms 18, 32-41.

Kohn, A.D., Summers, S.A., Birnbaum, M.J., and Roth, R.A. (1996). Expression of a constitutively active Akt Ser/Thr kinase in 3T3-L1 adipocytes stimulates glucose uptake and glucose transporter 4 translocation. The Journal of biological chemistry 271, 31372-31378.

Kopnin, P.B., Agapova, L.S., Kopnin, B.P., and Chumakov, P.M. (2007). Repression of sestrin family genes contributes to oncogenic Ras-induced reactive oxygen species up-regulation and genetic instability. Cancer research 67, 4671-4678.

Koppenol, W.H., Bounds, P.L., and Dang, C.V. (2011). Otto Warburg's contributions to current concepts of cancer metabolism. Nature reviews Cancer 11, 325-337.

Koritzinsky, M., Levitin, F., van den Beucken, T., Rumantir, R.A., Harding, N.J., Chu, K.C., Boutros, P.C., Braakman, I., and Wouters, B.G. (2013). Two phases of disulfide bond formation have differing requirements for oxygen. J Cell Biol 203, 615-627.

Kouroku, Y., Fujita, E., Tanida, I., Ueno, T., Isoai, A., Kumagai, H., Ogawa, S., Kaufman, R.J., Kominami, E., and Momoi, T. (2007). ER stress (PERK/eIF2alpha phosphorylation) mediates the polyglutamine-induced LC3 conversion, an essential step for autophagy formation. Cell Death Differ 14, 230-239.

Kroczynska, B., Kaur, S., Katsoulidis, E., Majchrzak-Kita, B., Sassano, A., Kozma, S.C., Fish, E.N., and Platanias, L.C. (2009). Interferon-dependent engagement of eukaryotic initiation factor 4B via S6 kinase (S6K)- and ribosomal protein S6K-mediated signals. Molecular and cellular biology 29, 2865-2875.

Kumimoto, H., Yamane, Y., Nishimoto, Y., Fukami, H., Shinoda, M., Hatooka, S., and Ishizaki, K. (2004). Frequent somatic mutations of mitochondrial DNA in esophageal squamous cell carcinoma. International journal of cancer Journal international du cancer 108, 228-231.

Lamming, D.W., Ye, L., Katajisto, P., Goncalves, M.D., Saitoh, M., Stevens, D.M., Davis, J.G., Salmon, A.B., Richardson, A., Ahima, R.S., et al. (2012). Rapamycin-induced insulin resistance is mediated by mTORC2 loss and uncoupled from longevity. Science 335, 1638-1643.

Laplante, M., and Sabatini, D.M. (2012). mTOR Signaling in Growth Control and Disease. Cell 149, 274-293.

Larman, T.C., DePalma, S.R., Hadjipanayis, A.G., Protopopov, A., Zhang, J., Gabriel, S.B., Chin, L., Seidman, C.E., Kucherlapati, R., and Seidman, J.G. (2012). Spectrum of somatic mitochondrial mutations in five cancers. Proceedings of the National Academy of Sciences of the United States of America 109, 14087-14091.

Lee, J.W., Park, S., Takahashi, Y., and Wang, H.G. (2010). The association of AMPK with ULK1 regulates autophagy. PloS one 5, e15394.

Leslie, N.R., Bennett, D., Lindsay, Y.E., Stewart, H., Gray, A., and Downes, C.P. (2003). Redox regulation of PI 3-kinase signalling via inactivation of PTEN. The EMBO journal 22, 5501-5510.

Levy, S., Avni, D., Hariharan, N., Perry, R.P., and Meyuhas, O. (1991). Oligopyrimidine tract at the 5' end of mammalian ribosomal protein mRNAs is required for their translational control. Proceedings of the National Academy of Sciences of the United States of America 88, 3319-3323.

Li, G., Scull, C., Ozcan, L., and Tabas, I. (2010). NADPH oxidase links endoplasmic reticulum stress, oxidative stress, and PKR activation to induce apoptosis. J Cell Biol 191, 1113-1125.

Li, W., Petrimpol, M., Molle, K.D., Hall, M.N., Battegay, E.J., and Humar, R. (2007). Hypoxia-induced endothelial proliferation requires both mTORC1 and mTORC2. Circulation research 100, 79-87.

Liang, J., and Mills, G.B. (2013). AMPK: a contextual oncogene or tumor suppressor? Cancer research 73, 2929-2935.

Little, J.L., Wheeler, F.B., Fels, D.R., Koumenis, C., and Kridel, S.J. (2007). Inhibition of fatty acid synthase induces endoplasmic reticulum stress in tumor cells. Cancer research 67, 1262-1269.

Long, X., Lin, Y., Ortiz-Vega, S., Yonezawa, K., and Avruch, J. (2005). Rheb binds and regulates the mTOR kinase. CurrBiol 15, 702-713.

Loos, B., Engelbrecht, A.M., Lockshin, R.A., Klionsky, D.J., and Zakeri, Z. (2013). The variability of autophagy and cell death susceptibility: Unanswered questions. Autophagy 9, 1270-1285.

Lu, M., Lawrence, D.A., Marsters, S., Acosta-Alvear, D., Kimmig, P., Mendez, A.S., Paton, A.W., Paton, J.C., Walter, P., and Ashkenazi, A. (2014). Cell death. Opposing unfolded-protein-response signals converge on death receptor 5 to control apoptosis. Science 345, 98-101.

Luca, R., Averna, M., Zalfa, F., Vecchi, M., Bianchi, F., La Fata, G., Del Nonno, F., Nardacci, R., Bianchi, M., Nuciforo, P., et al. (2013). The fragile X protein binds mRNAs involved in cancer progression and modulates metastasis formation. EMBO molecular medicine 5, 1523-1536.

Ma, X.M., and Blenis, J. (2009). Molecular mechanisms of mTOR-mediated translational control. Nat Rev Mol Cell Biol 10, 307-318.

Majmundar, A.J., Wong, W.J., and Simon, M.C. (2010). Hypoxia-inducible factors and the response to hypoxic stress. Molecular cell 40, 294-309.

Malhotra, J.D., and Kaufman, R.J. (2007). Endoplasmic reticulum stress and oxidative stress: a vicious cycle or a double-edged sword? Antioxidants & redox signaling 9, 2277-2293.

Marciniak, S.J., Yun, C.Y., Oyadomari, S., Novoa, I., Zhang, Y., Jungreis, R., Nagata, K., Harding, H.P., and Ron, D. (2004). CHOP induces death by promoting protein synthesis and oxidation in the stressed endoplasmic reticulum. Genes & development 18, 3066-3077.

Marino, G., Niso-Santano, M., Baehrecke, E.H., and Kroemer, G. (2014). Self-consumption: the interplay of autophagy and apoptosis. Nat Rev Mol Cell Biol 15, 81-94.

Mashima, T., Seimiya, H., and Tsuruo, T. (2009). De novo fatty-acid synthesis and related pathways as molecular targets for cancer therapy. British journal of cancer 100, 1369-1372.

Matsuki, H., Takahashi, M., Higuchi, M., Makokha, G.N., Oie, M., and Fujii, M. (2013). Both G3BP1 and G3BP2 contribute to stress granule formation. Genes to cells : devoted to molecular & cellular mechanisms 18, 135-146.

McEwen, E., Kedersha, N., Song, B., Scheuner, D., Gilks, N., Han, A., Chen, J.J., Anderson, P., and Kaufman, R.J. (2005). Heme-regulated inhibitor kinase-mediated phosphorylation of eukaryotic translation initiation factor 2 inhibits translation, induces stress granule formation, and mediates survival upon arsenite exposure. The Journal of biological chemistry 280, 16925-16933.

Menendez-Benito, V., Verhoef, L.G., Masucci, M.G., and Dantuma, N.P. (2005). Endoplasmic reticulum stress compromises the ubiquitin-proteasome system. Hum Mol Genet 14, 2787-2799.

Menon, S., Dibble, C.C., Talbott, G., Hoxhaj, G., Valvezan, A.J., Takahashi, H., Cantley, L.C., and Manning, B.D. (2014). Spatial control of the TSC complex integrates insulin and nutrient regulation of mTORC1 at the lysosome. Cell 156, 771-785.

Mercer, C.A., Kaliappan, A., and Dennis, P.B. (2009). A novel, human Atg13 binding protein, Atg101, interacts with ULK1 and is essential for macroautophagy. Autophagy 5, 649-662.

Miloslavski, R., Cohen, E., Avraham, A., Iluz, Y., Hayouka, Z., Kasir, J., Mudhasani, R., Jones, S.N., Cybulski, N., Ruegg, M.A., et al. (2014). Oxygen sufficiency controls TOP mRNA translation via the TSC-Rheb-mTOR pathway in a 4E-BP-independent manner. J Mol Cell Biol 6, 255-266.

Modica-Napolitano, J.S., and Singh, K.K. (2004). Mitochondrial dysfunction in cancer. Mitochondrion 4, 755-762.

Moeller, B.J., Cao, Y., Li, C.Y., and Dewhirst, M.W. (2004). Radiation activates HIF-1 to regulate vascular radiosensitivity in tumors: role of reoxygenation, free radicals, and stress granules. Cancer cell 5, 429-441.

Moon, J.C., Hah, Y.S., Kim, W.Y., Jung, B.G., Jang, H.H., Lee, J.R., Kim, S.Y., Lee, Y.M., Jeon, M.G., Kim, C.W., et al. (2005). Oxidative stress-dependent structural and functional switching of a human 2-Cys peroxiredoxin isotype II that enhances HeLa cell resistance to H2O2-induced cell death. The Journal of biological chemistry 280, 28775-28784.

Morita, M., Gravel, S.P., Chenard, V., Sikstrom, K., Zheng, L., Alain, T., Gandin, V., Avizonis, D., Arguello, M., Zakaria, C., et al. (2013). mTORC1 controls mitochondrial activity and biogenesis through 4E-BP-dependent translational regulation. Cell Metab 18, 698-711.

Mounir, Z., Krishnamoorthy, J.L., Wang, S., Papadopoulou, B., Campbell, S., Muller, W.J., Hatzoglou, M., and Koromilas, A.E. (2011). Akt determines cell fate through inhibition of the PERK-eIF2alpha phosphorylation pathway. Science signaling 4, ra62.

Muders, M.H., Zhang, H., Wang, E., Tindall, D.J., and Datta, K. (2009). Vascular endothelial growth factor-C protects prostate cancer cells from oxidative stress by the activation of mammalian target of rapamycin complex-2 and AKT-1. Cancer research 69, 6042-6048.

Myers, M.G., Jr., Grammer, T.C., Wang, L.M., Sun, X.J., Pierce, J.H., Blenis, J., and White, M.F. (1994). Insulin receptor substrate-1 mediates phosphatidylinositol 3'-kinase and p70S6k signaling during insulin, insulin-like growth factor-1, and interleukin-4 stimulation. The Journal of biological chemistry 269, 28783-28789.

Nascimento, E.B., Snel, M., Guigas, B., van der Zon, G.C., Kriek, J., Maassen, J.A., Jazet, I.M., Diamant, M., and Ouwens, D.M. (2010). Phosphorylation of PRAS40 on Thr246 by PKB/AKT facilitates efficient phosphorylation of Ser183 by mTORC1. Cell Signal 22, 961-967.

Nijholt, D.A., de Graaf, T.R., van Haastert, E.S., Oliveira, A.O., Berkers, C.R., Zwart, R., Ovaa, H., Baas, F., Hoozemans, J.J., and Scheper, W. (2011). Endoplasmic reticulum stress activates autophagy but not the proteasome in neuronal cells: implications for Alzheimer's disease. Cell Death Differ 18, 1071-1081.

Ogata, M., Hino, S., Saito, A., Morikawa, K., Kondo, S., Kanemoto, S., Murakami, T., Taniguchi, M., Tanii, I., Yoshinaga, K., et al. (2006). Autophagy is activated for cell survival after endoplasmic reticulum stress. Molecular and cellular biology 26, 9220-9231.

Oh, W.J., and Jacinto, E. (2011). mTOR complex 2 signaling and functions. Cell cycle 10, 2305-2316.

Ohoka, N., Yoshii, S., Hattori, T., Onozaki, K., and Hayashi, H. (2005). TRB3, a novel ER stress-inducible gene, is induced via ATF4-CHOP pathway and is involved in cell death. The EMBO journal 24, 1243-1255.

Oshiro, N., Takahashi, R., Yoshino, K., Tanimura, K., Nakashima, A., Eguchi, S., Miyamoto, T., Hara, K., Takehana, K., Avruch, J., et al. (2007). The proline-rich Akt substrate of 40 kDa (PRAS40) is a physiological substrate of mammalian target of rapamycin complex 1. The Journal of biological chemistry 282, 20329-20339.

Ozcan, U., Ozcan, L., Yilmaz, E., Duvel, K., Sahin, M., Manning, B.D., and Hotamisligil, G.S. (2008). Loss of the tuberous sclerosis complex tumor suppressors triggers the unfolded protein response to regulate insulin signaling and apoptosis. Molecular cell 29, 541-551.

Papandreou, I., Lim, A.L., Laderoute, K., and Denko, N.C. (2008). Hypoxia signals autophagy in tumor cells via AMPK activity, independent of HIF-1, BNIP3, and BNIP3L. Cell Death Differ 15, 1572-1581.

Parrott, L.A., and Templeton, D.J. (1999). Osmotic stress inhibits p70/85 S6 kinase through activation of a protein phosphatase. The Journal of biological chemistry 274, 24731-24736.

Pattingre, S., Bauvy, C., Carpentier, S., Levade, T., Levine, B., and Codogno, P. (2009). Role of JNK1-dependent Bcl-2 phosphorylation in ceramide-induced macroautophagy. The Journal of biological chemistry 284, 2719-2728.

Pattingre, S., Tassa, A., Qu, X., Garuti, R., Liang, X.H., Mizushima, N., Packer, M., Schneider, M.D., and Levine, B. (2005). Bcl-2 antiapoptotic proteins inhibit Beclin 1-dependent autophagy. Cell 122, 927-939.

Patursky-Polischuk, I., Stolovich-Rain, M., Hausner-Hanochi, M., Kasir, J., Cybulski, N., Avruch, J., Ruegg, M.A., Hall, M.N., and Meyuhas, O. (2009). The TSC-mTOR pathway mediates translational activation of TOP mRNAs by insulin largely in a raptor- or rictor-independent manner. Molecular and cellular biology 29, 640-649.

Pike, L.R., Singleton, D.C., Buffa, F., Abramczyk, O., Phadwal, K., Li, J.L., Simon, A.K., Murray, J.T., and Harris, A.L. (2013). Transcriptional up-regulation of ULK1 by ATF4 contributes to cancer cell survival. The Biochemical journal 449, 389-400.

Pizer, E.S., Jackisch, C., Wood, F.D., Pasternack, G.R., Davidson, N.E., and Kuhajda, F.P. (1996). Inhibition of fatty acid synthesis induces programmed cell death in human breast cancer cells. Cancer research 56, 2745-2747.

Porstmann, T., Griffiths, B., Chung, Y.L., Delpuech, O., Griffiths, J.R., Downward, J., and Schulze, A. (2005). PKB/Akt induces transcription of enzymes involved in cholesterol and fatty acid biosynthesis via activation of SREBP. Oncogene 24, 6465-6481.

Porstmann, T., Santos, C.R., Griffiths, B., Cully, M., Wu, M., Leevers, S., Griffiths, J.R., Chung, Y.L., and Schulze, A. (2008). SREBP activity is regulated by mTORC1 and contributes to Akt-dependent cell growth. Cell Metab 8, 224-236.

Possik, E., Jalali, Z., Nouet, Y., Yan, M., Gingras, M.C., Schmeisser, K., Panaite, L., Dupuy, F., Kharitidi, D., Chotard, L., et al. (2014). Folliculin regulates ampk-dependent autophagy and metabolic stress survival. PLoS genetics 10, e1004273.

Prostko, C.R., Brostrom, M.A., and Brostrom, C.O. (1993). Reversible phosphorylation of eukaryotic initiation factor 2 alpha in response to endoplasmic reticular signaling. Molecular and cellular biochemistry 127-128, 255-265.

Qin, L., Wang, Z., Tao, L., and Wang, Y. (2010). ER stress negatively regulates AKT/TSC/mTOR pathway to enhance autophagy. Autophagy 6, 239-247.

Ramirez-Valle, F., Braunstein, S., Zavadil, J., Formenti, S.C., and Schneider, R.J. (2008). eIF4GI links nutrient sensing by mTOR to cell proliferation and inhibition of autophagy. J Cell Biol 181, 293-307.

Raught, B., Peiretti, F., Gingras, A.C., Livingstone, M., Shahbazian, D., Mayeur, G.L., Polakiewicz, R.D., Sonenberg, N., and Hershey, J.W. (2004). Phosphorylation of eucaryotic translation initiation factor 4B Ser422 is modulated by S6 kinases. The EMBO journal 23, 1761-1769.

Robitaille, A.M., Christen, S., Shimobayashi, M., Cornu, M., Fava, L.L., Moes, S., Prescianotto-Baschong, C., Sauer, U., Jenoe, P., and Hall, M.N. (2013). Quantitative phosphoproteomics reveal mTORC1 activates de novo pyrimidine synthesis. Science 339, 1320-1323.

Rouschop, K.M., Dubois, L.J., Keulers, T.G., van den Beucken, T., Lambin, P., Bussink, J., van der Kogel, A.J., Koritzinsky, M., and Wouters, B.G. (2013). PERK/eIF2alpha signaling protects therapy resistant hypoxic cells through induction of glutathione synthesis and protection against ROS. Proceedings of the National Academy of Sciences of the United States of America 110, 4622-4627.

Rouschop, K.M., van den Beucken, T., Dubois, L., Niessen, H., Bussink, J., Savelkouls, K., Keulers, T., Mujcic, H., Landuyt, W., Voncken, J.W., et al. (2010). The unfolded protein response protects human tumor cells during hypoxia through regulation of the autophagy genes MAP1LC3B and ATG5. The Journal of clinical investigation 120, 127-141.

Rubsamen, D., Blees, J.S., Schulz, K., Doring, C., Hansmann, M.L., Heide, H., Weigert, A., Schmid, T., and Brune, B. (2012). IRES-dependent translation of egr2 is induced under inflammatory conditions. RNA 18, 1910-1920.

Rzymski, T., Milani, M., Pike, L., Buffa, F., Mellor, H.R., Winchester, L., Pires, I., Hammond, E., Ragoussis, I., and Harris, A.L. (2010). Regulation of autophagy by ATF4 in response to severe hypoxia. Oncogene 29, 4424-4435.

Sakamoto, T., Weng, J.S., Hara, T., Yoshino, S., Kozuka-Hata, H., Oyama, M., and Seiki, M. (2014). Hypoxia-inducible factor 1 regulation through cross talk between mTOR and MT1-MMP. Molecular and cellular biology 34, 30-42.

Salazar, M., Carracedo, A., Salanueva, I.J., Hernandez-Tiedra, S., Lorente, M., Egia, A., Vazquez, P., Blazquez, C., Torres, S., Garcia, S., et al. (2009). Cannabinoid action induces autophagy-mediated cell death through stimulation of ER stress in human glioma cells. The Journal of clinical investigation 119, 1359-1372.

Sancak, Y., Peterson, T.R., Shaul, Y.D., Lindquist, R.A., Thoreen, C.C., Bar-Peled, L., and Sabatini, D.M. (2008). The Rag GTPases bind raptor and mediate amino acid signaling to mTORC1. Science 320, 1496-1501.

Sancak, Y., Thoreen, C.C., Peterson, T.R., Lindquist, R.A., Kang, S.A., Spooner, E., Carr, S.A., and Sabatini, D.M. (2007). PRAS40 is an insulin-regulated inhibitor of the mTORC1 protein kinase. MolCell 25, 903-915.

Sarbassov, D.D., Ali, S.M., Sengupta, S., Sheen, J.H., Hsu, P.P., Bagley, A.F., Markhard, A.L., and Sabatini, D.M. (2006). Prolonged rapamycin treatment inhibits mTORC2 assembly and Akt/PKB. MolCell 22, 159-168.

Schieke, S.M., Phillips, D., McCoy, J.P., Jr., Aponte, A.M., Shen, R.F., Balaban, R.S., and Finkel, T. (2006). The mammalian target of rapamycin (mTOR) pathway regulates mitochondrial oxygen consumption and oxidative capacity. The Journal of biological chemistry 281, 27643-27652.

Schuck, S., Prinz, W.A., Thorn, K.S., Voss, C., and Walter, P. (2009). Membrane expansion alleviates endoplasmic reticulum stress independently of the unfolded protein response. J Cell Biol 187, 525-536.

Seguin, S.J., Morelli, F.F., Vinet, J., Amore, D., De Biasi, S., Poletti, A., Rubinsztein, D.C., and Carra, S. (2014). Inhibition of autophagy, lysosome and VCP function impairs stress granule assembly. Cell Death Differ.

Semenza, G.L. (2010). HIF-1: upstream and downstream of cancer metabolism. Current opinion in genetics & development 20, 51-56.

Shah, O.J., Wang, Z., and Hunter, T. (2004). Inappropriate activation of the TSC/Rheb/mTOR/S6K cassette induces IRS1/2 depletion, insulin resistance, and cell survival deficiencies. CurrBiol 14, 1650-1656.

Shimobayashi, M., and Hall, M.N. (2014). Making new contacts: the mTOR network in metabolism and signalling crosstalk. Nat Rev Mol Cell Biol 15, 155-162.

Singhapol, C., Pal, D., Czapiewski, R., Porika, M., Nelson, G., and Saretzki, G.C. (2013). Mitochondrial telomerase protects cancer cells from nuclear DNA damage and apoptosis. PloS one 8, e52989.

Sofer, A., Lei, K., Johannessen, C.M., and Ellisen, L.W. (2005). Regulation of mTOR and cell growth in response to energy stress by REDD1. Molecular and cellular biology 25, 5834-5845.

Sosa, V., Moline, T., Somoza, R., Paciucci, R., Kondoh, H., and ME, L.L. (2013). Oxidative stress and cancer: an overview. Ageing research reviews 12, 376-390.

Spitz, D.R., Sim, J.E., Ridnour, L.A., Galoforo, S.S., and Lee, Y.J. (2000). Glucose deprivation-induced oxidative stress in human tumor cells. A fundamental defect in metabolism? Annals of the New York Academy of Sciences 899, 349-362.

Szablewski, L. (2013). Expression of glucose transporters in cancers. Biochimica et biophysica acta 1835, 164-169.

Tagliavacca, L., Caretti, A., Bianciardi, P., and Samaja, M. (2012). In vivo up-regulation of the unfolded protein response after hypoxia. Biochimica et biophysica acta 1820, 900-906.

Takahara, T., and Maeda, T. (2012). Transient sequestration of TORC1 into stress granules during heat stress. Molecular cell 47, 242-252.

Takahashi, M., Higuchi, M., Matsuki, H., Yoshita, M., Ohsawa, T., Oie, M., and Fujii, M. (2013). Stress granules inhibit apoptosis by reducing reactive oxygen species production. Molecular and cellular biology 33, 815-829.

Tan, C.Y., and Hagen, T. (2013). mTORC1 dependent regulation of REDD1 protein stability. PloS one 8, e63970.

Tang, H., Hornstein, E., Stolovich, M., Levy, G., Livingstone, M., Templeton, D., Avruch, J., and Meyuhas, O. (2001). Amino acid-induced translation of TOP mRNAs is fully dependent on phosphatidylinositol 3-kinase-mediated signaling, is partially inhibited by rapamycin, and is independent of S6K1 and rpS6 phosphorylation. MolCell Biol 21, 8671-8683.

Tcherkezian, J., Cargnello, M., Romeo, Y., Huttlin, E.L., Lavoie, G., Gygi, S.P., and Roux, P.P. (2014). Proteomic analysis of cap-dependent translation identifies LARP1 as a key regulator of 5'TOP mRNA translation. Genes & development 28, 357-371.

Thedieck, K., Holzwarth, B., Prentzell, M.T., Boehlke, C., Klasener, K., Ruf, S., Sonntag, A.G., Maerz, L., Grellscheid, S.N., Kremmer, E., et al. (2013). Inhibition of mTORC1 by astrin and stress granules prevents apoptosis in cancer cells. Cell 154, 859-874.

Thedieck, K., Polak, P., Kim, M.L., Molle, K.D., Cohen, A., Jeno, P., Arrieumerlou, C., and Hall, M.N. (2007). PRAS40 and PRR5-like protein are new mTOR interactors that regulate apoptosis. PloS one 2, e1217.

Thomas, M.G., Loschi, M., Desbats, M.A., and Boccaccio, G.L. (2011). RNA granules: the good, the bad and the ugly. Cell Signal 23, 324-334.

Thoreen, C.C., Chantranupong, L., Keys, H.R., Wang, T., Gray, N.S., and Sabatini, D.M. (2012). A unifying model for mTORC1-mediated regulation of mRNA translation. Nature 485, 109-113.

Toschi, A., Lee, E., Gadir, N., Ohh, M., and Foster, D.A. (2008). Differential dependence of hypoxia-inducible factors 1 alpha and 2 alpha on mTORC1 and mTORC2. The Journal of biological chemistry 283, 34495-34499.

Tourriere, H., Chebli, K., Zekri, L., Courselaud, B., Blanchard, J.M., Bertrand, E., and Tazi, J. (2003). The RasGAP-associated endoribonuclease G3BP assembles stress granules. J Cell Biol 160, 823-831.

Trachootham, D., Alexandre, J., and Huang, P. (2009). Targeting cancer cells by ROS-mediated mechanisms: a radical therapeutic approach? Nat Rev Drug Discov 8, 579-591.

Tracy, K., Dibling, B.C., Spike, B.T., Knabb, J.R., Schumacker, P., and Macleod, K.F. (2007). BNIP3 is an RB/E2F target gene required for hypoxia-induced autophagy. Molecular and cellular biology 27, 6229-6242.

Tsun, Z.Y., Bar-Peled, L., Chantranupong, L., Zoncu, R., Wang, T., Kim, C., Spooner, E., and Sabatini, D.M. (2013). The folliculin tumor suppressor is a GAP for the RagC/D GTPases that signal amino acid levels to mTORC1. Molecular cell 52, 495-505.

Tu, B.P., and Weissman, J.S. (2002). The FAD- and O(2)-dependent reaction cycle of Ero1-mediated oxidative protein folding in the endoplasmic reticulum. Molecular cell 10, 983-994.

Vafa, O., Wade, M., Kern, S., Beeche, M., Pandita, T.K., Hampton, G.M., and Wahl, G.M. (2002). c-Myc can induce DNA damage, increase reactive oxygen species, and mitigate p53 function: a mechanism for oncogene-induced genetic instability. Molecular cell 9, 1031-1044.

Valk, K., Vooder, T., Kolde, R., Reintam, M.A., Petzold, C., Vilo, J., and Metspalu, A. (2010). Gene expression profiles of non-small cell lung cancer: survival prediction and new biomarkers. Oncology 79, 283-292.

van der Sanden, M.H., Houweling, M., van Golde, L.M., and Vaandrager, A.B. (2003). Inhibition of phosphatidylcholine synthesis induces expression of the endoplasmic reticulum stress and apoptosis-related protein CCAAT/enhancer-binding protein-homologous protein (CHOP/GADD153). The Biochemical journal 369, 643-650.

Vander Haar, E., Lee, S.I., Bandhakavi, S., Griffin, T.J., and Kim, D.H. (2007). Insulin signalling to mTOR mediated by the Akt/PKB substrate PRAS40. NatCell Biol 9, 316-323.

Vattem, K.M., and Wek, R.C. (2004). Reinitiation involving upstream ORFs regulates ATF4 mRNA translation in mammalian cells. Proceedings of the National Academy of Sciences of the United States of America 101, 11269-11274.

Wang, L., Harris, T.E., and Lawrence, J.C., Jr. (2008). Regulation of proline-rich Akt substrate of 40 kDa (PRAS40) function by mammalian target of rapamycin complex 1 (mTORC1)-mediated phosphorylation. The Journal of biological chemistry 283, 15619-15627.

Wang, R.H., Kim, H.S., Xiao, C., Xu, X., Gavrilova, O., and Deng, C.X. (2011). Hepatic Sirt1 deficiency in mice impairs mTorc2/Akt signaling and results in hyperglycemia, oxidative damage, and insulin resistance. The Journal of clinical investigation 121, 4477-4490.

Wang, X., and Proud, C.G. (1997). p70 S6 kinase is activated by sodium arsenite in adult rat cardiomyocytes: roles for phosphatidylinositol 3-kinase and p38 MAP kinase. Biochem Biophys Res Commun 238, 207-212.

Warburg, O. (1956). On the origin of cancer cells. Science 123, 309-314.

Watson, J. (2013). Oxidants, antioxidants and the current incurability of metastatic cancers. Open biology 3, 120144.

Wei, Y., Pattingre, S., Sinha, S., Bassik, M., and Levine, B. (2008). JNK1-mediated phosphorylation of Bcl-2 regulates starvation-induced autophagy. Molecular cell 30, 678-688.

Wek, S.A., Zhu, S., and Wek, R.C. (1995). The histidyl-tRNA synthetase-related sequence in the eIF-2 alpha protein kinase GCN2 interacts with tRNA and is required for activation in response to starvation for different amino acids. Molecular and cellular biology 15, 4497-4506.

Weyemi, U., Lagente-Chevallier, O., Boufraqech, M., Prenois, F., Courtin, F., Caillou, B., Talbot, M., Dardalhon, M., Al Ghuzlan, A., Bidart, J.M., et al. (2012). ROS-generating NADPH oxidase NOX4 is a critical mediator in oncogenic H-Ras-induced DNA damage and subsequent senescence. Oncogene 31, 1117-1129.

Wilson, W.R., and Hay, M.P. (2011). Targeting hypoxia in cancer therapy. Nature reviews Cancer 11, 393-410.

Win, S., Than, T.A., Fernandez-Checa, J.C., and Kaplowitz, N. (2014). JNK interaction with Sab mediates ER stress induced inhibition of mitochondrial respiration and cell death. Cell death & disease 5, e989.

Wippich, F., Bodenmiller, B., Trajkovska, M.G., Wanka, S., Aebersold, R., and Pelkmans, L. (2013). Dual specificity kinase DYRK3 couples stress granule condensation/dissolution to mTORC1 signaling. Cell 152, 791-805.

Woo, D.K., Green, P.D., Santos, J.H., D'Souza, A.D., Walther, Z., Martin, W.D., Christian, B.E., Chandel, N.S., and Shadel, G.S. (2012). Mitochondrial genome instability and ROS enhance intestinal tumorigenesis in APC(Min/+) mice. The American journal of pathology 180, 24-31.

Yakes, F.M., and Van Houten, B. (1997). Mitochondrial DNA damage is more extensive and persists longer than nuclear DNA damage in human cells following oxidative stress. Proceedings of the National Academy of Sciences of the United States of America 94, 514-519.

Yamamoto, K., Sato, T., Matsui, T., Sato, M., Okada, T., Yoshida, H., Harada, A., and Mori, K. (2007). Transcriptional induction of mammalian ER quality control proteins is mediated by single or combined action of ATF6alpha and XBP1. Developmental cell 13, 365-376.

Yamasaki, S., and Anderson, P. (2008). Reprogramming mRNA translation during stress. Curr Opin Cell Biol 20, 222-226.

Yang, Z.J., Chee, C.E., Huang, S., and Sinicrope, F.A. (2011). The role of autophagy in cancer: therapeutic implications. Molecular cancer therapeutics 10, 1533-1541.

Yecies, J.L., and Manning, B.D. (2011). mTOR links oncogenic signaling to tumor cell metabolism. Journal of molecular medicine 89, 221-228.

Yecies, J.L., Zhang, H.H., Menon, S., Liu, S., Yecies, D., Lipovsky, A.I., Gorgun, C., Kwiatkowski, D.J., Hotamisligil, G.S., Lee, C.H., et al. (2011). Akt stimulates hepatic SREBP1c and lipogenesis through parallel mTORC1-dependent and independent pathways. Cell Metab 14, 21-32.

Yoshida, H., Haze, K., Yanagi, H., Yura, T., and Mori, K. (1998). Identification of the cis-acting endoplasmic reticulum stress response element responsible for transcriptional induction of mammalian glucose-regulated proteins. Involvement of basic leucine zipper transcription factors. The Journal of biological chemistry 273, 33741-33749.

Yoshida, S., Hong, S., Suzuki, T., Nada, S., Mannan, A.M., Wang, J., Okada, M., Guan, K.L., and Inoki, K. (2011). Redox regulates mammalian target of rapamycin complex 1 (mTORC1) activity by modulating the TSC1/TSC2-Rheb GTPase pathway. The Journal of biological chemistry 286, 32651-32660.

Young, C.D., Lewis, A.S., Rudolph, M.C., Ruehle, M.D., Jackman, M.R., Yun, U.J., Ilkun, O., Pereira, R., Abel, E.D., and Anderson, S.M. (2011). Modulation of glucose transporter 1 (GLUT1) expression levels alters mouse mammary tumor cell growth in vitro and in vivo. PloS one 6, e23205.

Yu, Y., Yoon, S.O., Poulogiannis, G., Yang, Q., Ma, X.M., Villen, J., Kubica, N., Hoffman, G.R., Cantley, L.C., Gygi, S.P., et al. (2011). Phosphoproteomic analysis identifies Grb10 as an mTORC1 substrate that negatively regulates insulin signaling. Science 332, 1322-1326.

Zhang, J., Kim, J., Alexander, A., Cai, S., Tripathi, D.N., Dere, R., Tee, A.R., Tait-Mulder, J., Di Nardo, A., Han, J.M., et al. (2013). A tuberous sclerosis complex signalling node at the peroxisome regulates mTORC1 and autophagy in response to ROS. Nat Cell Biol 15, 1186-1196.

Zheng, M., Wang, Y.H., Wu, X.N., Wu, S.Q., Lu, B.J., Dong, M.Q., Zhang, H., Sun, P., Lin, S.C., Guan, K.L., et al. (2011). Inactivation of Rheb by PRAK-mediated phosphorylation is essential for energy-depletion-induced suppression of mTORC1. Nat Cell Biol 13, 263-272.