Crosstalk of the mTOR network with stress granules and the TGF-beta pathway

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CHAPTER 2

Molecular mechanisms of mTOR regulation by stress

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ABSTRACT

Tumors are prime examples of cell growth in unfavorable environments that elicit cellular stress. The high metabolic demand and insufficient vascularization of tumors cause a deficiency of oxygen and nutrients. Oncogenic mutations map to signaling events via 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 the mechanisms contributing to mTOR regulation by stress and suggest a model wherein stress granules function as guardians of mTORC1 signaling, allowing cancer cells to escape stress-induced cell death.

Keywords: apoptosis, balance, cancer, cell death, ER stress, hypoxia, hyperactivation, mammalian target of rapamycin, mTORC1, mTORC2, oxidative stress, RNA granules, stress granules, survival

Abbreviations

4E-BP1	4E-binding protein 1
5′TOP	5′ terminal oligopyrimidine
AMPK	AMP-activated protein kinase
ATF4	activating transcription factor 4
ATF6	activating transcription factor 6
ATG	autophagy regulated protein
ATM	ataxia telangiectasia mutated
CAD	carbamoyl-phosphate synthetase 2, aspartate transcarbamylase, and dihydroorotase
CaMKKbeta	calmodulin-dependent protein kinase kinase β
CMA	chaperon-mediated autophagy
DYRK3	dual specificity tyrosine-phosphorylation-regulated kinase 3
eIF2α	eukaryotic translation initiation factor 2α
eIF4B	eukaryotic translation initiation factor 4B
eIF4E	eukaryotic translation initiation factor 4E
ER	endoplasmic reticulum

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FIP200	FAK family kinase-interacting protein of 200 kDa
FLCN	folliculin
FMRP	fragile X mental retardation protein
FoxO1/3A	forkhead box O1/3A
G3BP	Ras-GTPase activating protein SH-3 domain binding protein
GAP	GTPase-activating protein
GCN2	general control nonderepressible 2
GLUT4	glucose transporter 4
Grb10	growth factor receptor-bound protein 10
GSK	glycogen synthase kinase
HIF	hypoxia inducible factor
hnRNP-A1	heterogeneous nuclear ribonucleoprotein A1
HRI	hemin-regulated inhibitor
HSF1	heat shock factor protein 1
Hsp70	70 kDa heat shock protein
IR	insulin receptor
Ire1	inositol-requiring protein 1
IRES	internal ribosomal entry sites
IRS	insulin receptor substrate
JNK	c-Jun NH(2)-terminal kinase
LARP1	La-related protein 1
LDH	lactate dehydrogenase
MAPK	mitogen activated protein kinase
mSin1	mammalian stress-activated protein kinase interacting protein 1
mtDNA	mitochondrial DNA
mTOR	mammalian target of rapamycin
mTORC1	mTOR complex 1
mTORC2	mTOR complex 2
NFL	negative feedback loop
NOX	NADPH oxidase
Nrf2	nuclear factor erythroid 2-like 2
PABP1	polyadenylate-binding protein 1
PDK1	3-phosphoinositide-dependent kinase-1
PERK	protein kinase RNA-like ER kinase
PI3K	phosphatidylinositol 3-kinases
PIP2	phosphatidylinositol-3,4-biphosphate
PIP3	phosphatidylinositol-3,4,5-triphosphate
PKR	double-stranded RNA activated protein kinase
PPP	pentose phosphate pathway

PTEN	phosphatase and tensin homolog
R5P	ribose-5-phosphate
raptor	regulatory associated protein of mTOR
RACK1	signaling scaffold protein receptor of activated protein kinase C 1
REDD1	regulated in development and DNA damage responses 1
rheb	ras-homolog-enriched-in-brain
rictor	rapamycin-insensitive companion of mTOR
ROS	reactive oxygen species
S6K	S6 kinase
SREBP	sterol regulatory element-binding protein
TCA cycle	tricarboxylic acid cycle
TIA-1	T cell intracellular antigen 1
TIAR	TIA-1-related protein
TNFα	tumor necrosis factor alpha
TRAF2	TNF receptor-associated factor 2
TRB3	tribbles homolog 3
TSC1	hamartin (tuberous sclerosis 1 protein)
TSC2	tuberin (tuberous sclerosis 2 protein)
ULK1	unc-51-like kinase
uORF	upstream open reading frame
UPR	unfolded protein response
USP10	ubiquitin-specific protease 10
VEGF	vascular endothelial growth factor

WHY DO CANCER CELLS PROFIT FROM MTOR ACTIVATION?

The mTOR signaling network (**Fig. 1**) is hyperactivated in many tumors (reviewed by Yecies et al.[1]). mTOR kinase is present in 2 multiprotein complexes, mTORC1 and mTORC2.[2] mTORC1 contains the essential specific scaffold protein regulatory associated protein of mTOR (raptor) and functions as a master regulator of cell growth and metabolism by favoring anabolic processes in the presence of nutrients and energy.[3,4] 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.[2]). mTORC2 senses nutrients and growth factors and modulates lipid and glucose metabolism[5] and cytoskeleton reorganization (reviewed by Oh et al.[6]). The cancer drug rapamycin directly binds and inhibits mTORC1, but can also have indirect long-term effects on mTORC2.[7,8]

Amino acids activate mTORC1 via the rag GTPases,[9,10] which function in conjunction with the guanine nucleotide exchange factor (GEF) ragulator complex[11] and the GTPase activating protein (GAP) folliculin (FLCN)[12] to modulate the translocation of mTORC1 to the lysosomal membrane in a glutaminolysis-dependent manner[13] (reviewed by Bar-Peled et al.[14]). At the lysosome, mTORC1 encounters the small GTPase ras-homolog-enriched-in-brain (rheb), which activates mTORC1 in response to growth factors (e.g., insulin).[15] Amino acid deprivation leads to recruitment of the hamartin (TSC1)–tuberin (TSC2) hetero-complex (TSC1–TSC2) to the lysosomal membrane in a rag GTPase-dependent manner.[16] The tumor suppressor TSC1–TSC2 functions as a GAP for the GTPase rheb and thereby inhibits mTORC1.[17]

Acting through insulin receptor substrate (IRS), the insulin receptor (IR) activates class I phosphatidylinositol 3-kinases (PI3K), whose subunits are often mutated in tumors. PI3K phosphorylates phosphatidylinositol-3,4-biphosphate (PIP2) to generate phosphatidylinositol-3,4,5-triphosphate (PIP3). Binding of PIP3 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 TSC1–TSC2 complex by phosphorylating TSC2; phosphorylation of TSC2 by Akt leads to dissociation of the TSC1–TSC2 complex from lysosomes[18] and enables mTORC1 activation. The PI3K antagonist phosphatase and tensin homolog (PTEN) is a tumor suppressor that counteracts growth factor-dependent mTORC1 activation by dephosphorylating PIP3 to generate PIP2 (reviewed by Laplante et al.[19]).
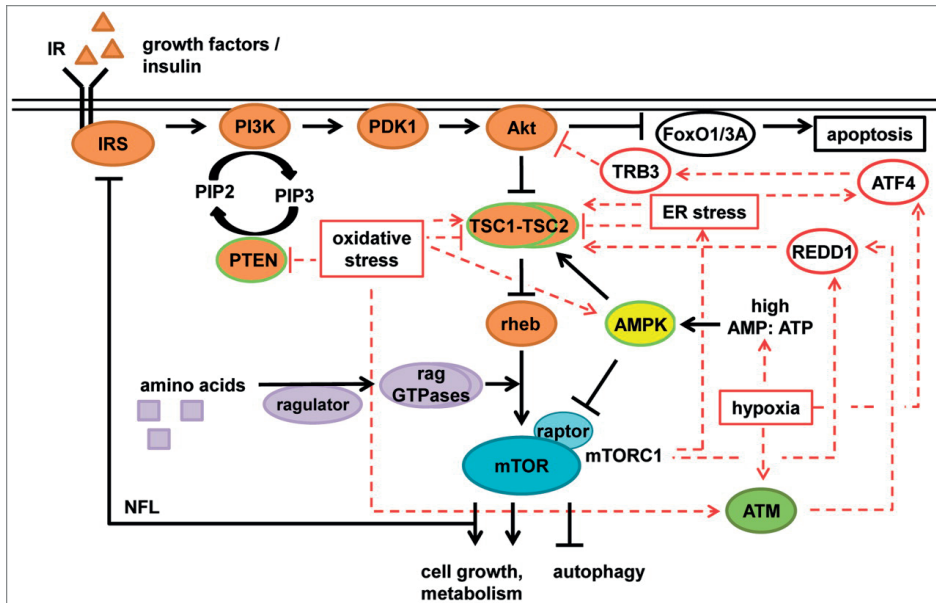
Figure 1. mTORC1 and stress. mTORC1 is regulated by amino acids, growth factors (i.e., insulin), and energy status (AMP:ATP). Amino acids are sensed by the ragulator complex and the rag GTPases, mediating re-localization of mTORC1 to lysosomes where it encounters rheb. Insulin activates the IR, which then activates the IRS. Active IRS induces PI3K, which converts PIP2 to PIP3. PIP3 accumulation results in the recruitment of PDK1 and Akt to the plasma membrane where 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 a high AMP:ATP ratio 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, which 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 also induces ATF4 translation, and activates AMPK. Induction of HIFs by hypoxia (via ATM) induces expression of REDD1, which activates the TSC1–TSC2 complex, inhibiting mTORC1. This results in a negative feedback loop, 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.

mTORC1 responds to cellular energy status via the heterotrimeric AMP-activated protein kinase (AMPK). AMPK is activated by 2 mechanisms. On the one hand, kinases such as the tumor suppressor kinase LKB1 and calmodulin-dependent protein kinase kinase β (CaMKKβ) 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[20]). AMPK inhibits

mTORC1 by phosphorylating raptor[21] and by an activating phosphorylation on TSC2.[22] 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.[23]

Cancer cell growth depends on ATP-demanding anabolic processes including protein, lipid, and nucleotide biosynthesis. mTORC1 controls ATP supply by inducing mitochondrial biogenesis, the tricarboxylic acid (TCA) cycle, and aerobic respiration.[24-26] Furthermore, mTORC1 promotes the delivery of substrates to the TCA cycle by inducing glucose uptake[27] and glutamine catabolism.[28] A major anabolic function of mTORC1 in cancer is its stimulating role in translation[29] (reviewed by Ma et al.[30]). 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 by which ribosomes reach the start codon. Furthermore, mTORC1 enhances the cellular protein biosynthesis capacity by activating ribosomal RNA (rRNA) transcription and processing[31] (reviewed by Iadevaia et al.[32]) and the biosynthesis of ribosomal proteins and elongation factors; these proteins are often encoded by transcripts that contain 5′ terminal oligopyrimidine (5′TOP) tracts,[33] whose translation depends on 4E-BP1 inactivation.[26,34] 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.[35] Furthermore, 5′TOP regulation by mTOR has been reported to also occur in a 4E-BP1- and mTORC1-independent manner,[36,37] in particular under hypoxic conditions.[37] S6 kinase (S6K), another mTORC1 substrate, phosphorylates S6[38] and the eIF4F component eukaryotic translation initiation factor 4B (eIF4B),[39,40] which may contribute to translational control by mTORC1 but not by translational regulation of 5′TOP mRNAs.[41] In addition, S6K promotes mRNA expression of ribosome biogenesis genes, thereby probably increasing overall translation capacity.[42] The PI3K–Akt–mTORC1 pathway upregulates the synthesis of lipids via the sterol regulatory element-binding protein (SREBP) transcription factors,[5,43-46] which regulate genes involved in lipid and sterol synthesis.[47] mTORC1 stimulates nucleotide biosynthesis via direct phosphorylation of the trifunctional enzyme carbamoyl-phosphate synthetase 2-aspartate transcarbamylase-dihydroorotase (CAD), which catalyzes the first 3 steps of *de novo* pyrimidine synthesis.[48,49] In addition, mTORC1 promotes the expression of genes encoding enzymes of the

oxidative branch of the pentose phosphate pathway (PPP),[45] 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 should, however, be noted that mTORC1 inhibits the oncogene Akt via negative feedback loops (NFLs) dependent on IRS[50–52] and growth factor receptor-bound protein 10 (Grb10)[53,54]. Akt inhibits apoptosis by inhibiting the transcription factor forkhead box O1/3A (FoxO1/3A).[55] Furthermore, Mounir et al.[56] 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 et al.[57]). Consequently, cancer cells need to balance mTORC1 activity to keep biosynthetic processes and Akt active at the same time.

mTOR Regulation by Stresses in Cancer Cells

The capacity for uncontrolled cellular growth and proliferation brings about challenges, such as certain stresses, that a tumor cell has to cope with in order to survive. Nutrient and oxygen depletion in conjunction with a hyperactive metabolism, mitochondrial dysfunction, and oncogenic mTOR signaling are common conditions in cancer cells[58–62] 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**).

mTORC1 under ER stress

Numerous studies report an accelerated unfolded protein response (UPR) in cancer cells. ER stress results from imbalances between protein synthesis and protein folding capacity that lead to accumulation of unfolded proteins in the ER lumen (reviewed by Clarke et al.[63] and Fels et al.[64]). 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.[64,65] Decreased glucose supply restricts ATP synthesis, which is required for chaperone activity in the ER (reviewed by Braakman et al.[66]). 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, and amino acids). Proliferating cells require lipids for membrane formation and ER expansion. A lipid shortage, and hence reduced membrane synthesis, can induce ER stress[67–69] and apoptosis.[70,71] These observa-

tions suggest that glucose limitation is a trigger for ER stress. However, studies on cancer metabolism have reported the Warburg effect, namely aerobic glycolysis and accumulation of lactate.[72,73] The Warburg effect is defined by an enhanced glycolytic rate under normoxic conditions. Cells that exhibit the Warburg effect consume glucose relatively rapidly and therefore require a sufficient supply of glucose.[74] These 2 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[75,76] allow the cell to take up as many nutrients as the environment allows. Enhanced glucose uptake, in conjunction with hyperactivation of the mTOR pathway, is prone to induce ER stress as increased protein synthesis can overwhelm the protein folding capacity of the ER.[63,77] In contrast, at advanced tumor stages the outgrowth from the vascular system results in nutrient shortage, which also leads 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 et al.[78]). The 3 sensors inositol-requiring protein 1 (Ire1), activating transcription factor 6 (ATF6), and PERK are membrane embedded proteins that synergistically re-establish ER homeostasis. For example, they induce chaperone synthesis[79,80] to increase protein folding capacity, and inhibit translation[81,82] to relieve protein overload. In addition, autophagy (see below) has emerged as the major mechanism for the clearance of misfolded proteins in the ER,[83,84] as ER stress suppresses proteasome-mediated degradation.[85,86] 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 et al.[57]) (**Fig. 1**). Mutations or knock out of the *TSC1* and *TSC2* genes that lead to mTORC1 hyperactivation sensitize cells to ER stress and apoptosis. This depends on mTORC1 as it can be reversed by raptor inhibition,[77,87] further supporting the notion 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-term periods of ER stress result in TSC1–TSC2 inactivation and subsequent mTORC1 activation, whereas prolonged stress activates the TSC1–TSC2 complex.[88] 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); this induces apoptosis by transcriptional activation of stress-related proteins, including tribbles homolog 3 (TRB3),[89] which inhibits Akt. In addition,

ER stress inhibits mTORC2 and its substrate Akt in a glycogen synthase kinase (GSK) 3-β–dependent manner.[90] Furthermore, activation of mTORC1 by ER stress inhibits Akt via the mTORC1-dependent NFLs, followed by activation of the Ire1–c-Jun NH(2)-terminal kinase (JNK) pathway, which in turn induces apoptosis.[91] This suggests that cancer cells under chronic ER stress must cope with Akt inactivation by multiple mechanisms.[89–91] As active mTORC188 contributes to Akt inhibition and apoptosis susceptibility,[77,87,88,91] cancer cells need to prevent mTORC1 hyperactivation to maintain sufficient Akt activity and ensure their survival under ER stress.

mTORC1 under hypoxia

The outgrowth of the tumor from the vascular system entails a shortage not only in glucose supply but also in oxygen (**Fig. 2**). This phenomenon is termed "hypoxia" and induces a stress response that can be monitored by upregulation of the hypoxia inducible factors (HIFs).[58] Oxygen shortage restricts the cellular capacity for ATP production because 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.[58]

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.[92]). The HIF transcription factors are key to the hypoxia-induced stress response. HIF1α induces gene products such as the vascular endothelial growth factors (VEGFs),[93] which activate growth of the vascular network (angiogenesis)[94] 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). In this case, HIFs can be induced by oncogenic signaling via mTORC1[95,96] 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,[97] but the underlying mechanisms and their potential interaction with mTOR signaling remain to be explored.
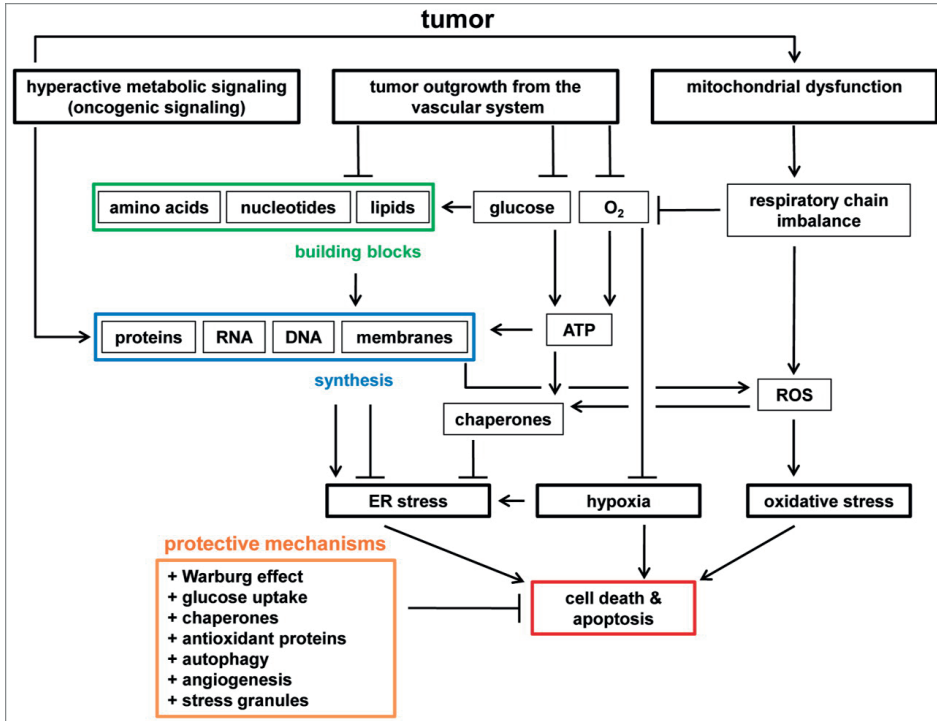
Figure 2. Stresses in tumors. Hyperactive metabolic signaling (e.g., induced by oncogenes) can result in increased synthesis of proteins, RNA, DNA, and membranes. Lipid synthesis is required for ER homeostasis, whereas hyperactive protein synthesis can induce ER stress. Tumors eventually outgrow the 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, for example 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 the induction of apoptosis by chronic stresses. Examples of such mechanisms are metabolic transformation (the Warburg effect), glucose uptake, chaperone and antioxidant protein synthesis, autophagy, angiogenesis, and stress granule formation.

Hypoxia inactivates mTORC1 by different mechanisms (**Fig. 1**). First, hypoxia increases the AMP:ATP ratio, which activates AMPK.[98,99] Second, hypoxia activates the DNA damage response protein ataxia telangiectasia mutated (ATM) in the cytosol in a DNA damage-independent manner.[100] ATM phosphorylates HIF1α, resulting in induction of regulated in development and DNA damage responses 1 (REDD1).[100] REDD1 and mTORC1 are connected via a NFL:

REDD1 inhibits mTORC1 via TSC1–TSC2 activation,[101–103] whereas mTORC1 is necessary to stabilize the REDD1 protein.[104,105] Furthermore, mTORC1 activity is also required for HIF1α expression.[95,106] Thus, hypoxic cells require mTORC1 to re-establish homeostasis through the HIF1α- and REDD1-dependent stress response. On the other hand, mTORC1 needs to be restricted, because 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.[107] Thus, hypoxia inhibitory and stimulatory inputs contribute to net mTORC1 activity.

mTORC1 under oxidative stress

A third challenge that is commonly encountered 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.[108] This not only increases ATP production but may also increase cellular ROS[108] as a result of temporary imbalances between reduction and oxidation at the level of Complexes I and III of the respiratory chain.[109] Also, dysfunction of mitochondria in cancer cells[110] may contribute to increased ROS levels. Mutations in cancer cells tend to accumulate in mitochondrial DNA (mtDNA)[111,112] and are enriched in genes coding for subunits of Complexes I, III, and IV of the electron transport chain,[113] 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.[114,115] Of note, ROS formation in cancer cells has been often linked with an induction of oncogenic signaling,[116] for example of the mitogen activated protein kinase (MAPK) and PTEN/Akt pathways.[117–120] For example, H-Ras activates the ROS-producing NADPH oxidase (NOX)[121] enzymes and suppresses the antioxidant molecule Sestrin 1.[122] Akt increases the activity of several respiratory complexes in a 4E-BP1-dependent manner,[120] thus increasing the potential for 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 the ROS themselves. ROS can oxidize cysteines, leading to disulfide bond formation in proteins and thereby altering their activity (reviewed by Groitl et al.[123]). Through 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.[124] 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 including chaperones, antioxidant enzymes, or proteins involved in the inflammatory and immune response (reviewed by Sosa et al.[108]). For example, cancer cells show upregulation of the antioxidative proteins glutathione, superoxide dismutase, catalase, and thioredoxin (reviewed by Watson et al.[125]), at least in part as a result of Nrf2-induced oncogenic signaling (reviewed by DeNicola et al.[126]).

Early evidence for the regulation of mTORC1 complex by ROS came from UV irradiation experiments. UV radiation activates mTORC1 during the first 7 hours, with a subsequent decrease over time,[127–129] and mTORC1 activation can be prevented by hydrogen peroxide scavengers.[129] Additionally, chemical treatments with hydrogen peroxide or sodium arsenite[130] affect mTORC1 in a dosage- and time-dependent manner. Generally speaking, short treatments and low concentrations seem to induce mTORC1, whereas prolonged treatments and high concentrations diminish or abolish mTORC1 activity.[131–134] It should be noted, however, that the dosage- and time-dependent effects of ROS on mTORC1 are highly context- and cell type-dependent. The tumor suppressor PTEN[135–137] is redox sensitive and directly inactivated by cysteine oxidation; in addition, TSC1–TSC2 has been suggested to be directly oxidized by ROS[138] (**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.[132] reported recently that mTORC1 can also be inactivated by ROS, and that this depends on peroxisomal localization of TSC2. Furthermore, ROS activates cytoplasmic ATM[139,140] and AMPK, which both inhibit mTORC1 (reviewed by Hardie et al.[99]). 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.

Regulation of mTORC2 by stresses

Relatively little is known about the response of mTORC2 to stress, therefore in this review we focus mostly on mTORC1. It should be noted, however, that increasing evidence additionally suggests mTORC2 as an important component of stress signaling. There are activating and inhibiting inputs on the mTORC2 network during different stresses. Examples are the inhibition of mTORC2 by ER stress[90] and oxidative stress,[141,142] and the activation of mTORC2 during hypoxia.[143] ER stress results in GSK3β-dependent phosphorylation of rictor, which decreases the affinity of mTORC2 for its substrates,[90] whereas oxidative stress

leads to mTORC2 disruption and inactivation.[141,142] The mechanism by which mTORC2 is activated during hypoxia is not understood. mTORC2 activation during hypoxia is needed for the hypoxia stress response as mTORC2 induces transcription of HIF1α and HIF2α,[106] and positively modulates hypoxia-induced proliferation.[143]

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,[73] 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 for disulphide bond formation (oxidative protein folding) within the ER.[144,145] Thus, hypoxia is able to induce ER stress.[146,147] Conversely, severe ER stress induces oxidative protein folding[148] that leads to ROS formation, which in a vicious cycle can lead to protein damage and reinforce the ER stress.[149] Furthermore, glucose starvation[150,151] and hypoxia[152,153] 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 thus have to cope with chronic stress conditions that are prone to induce apoptosis.[154–159] However, cancer cells acquire properties that enable them to escape programmed cell death[131,160,161] (see below).

REGULATION OF GLUCOSE AND PROTEIN HOMEOSTASIS BY MTORC1 DURING STRESS

Hyperactive biosynthesis in proliferating cells creates 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 2 ATP molecules and pyruvate. Under normoxic conditions, pyruvate is introduced into the TCA cycle, which theoretically generates 36 ATP molecules via aerobic respiration. 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).[72] 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 et al.[162]). This metabolic transformation, which was discovered by Otto Warburg nearly 100 years ago, is named the "Warburg effect."[72] Another shift of glucose

metabolism in cancer cells is induction of the PPP (reviewed by Sosa et al.[108]). Diverting carbon from glycolysis into the PPP supplies increases levels of (1) R5P for nucleotide synthesis, which is needed for DNA replication and transcription (reviewed by DeBerardinis et al.[163]); and (2) NADPH, which supplies electrons for biosynthesis and eliminates ROS, thereby providing protection from oxidative stress. Diversion of glucose into the PPP and thus into lactate is modulated by several mTOR network components that positively regulate glucose uptake and glycolysis: Akt promotes glucose uptake, for example, by stimulating translocation of glucose transporter 4 (GLUT4)[164,165] to the plasma membrane. Furthermore, AMPK inactivation is tumorigenic as AMPK inhibits the Warburg effect in a HIF1α-dependent manner.[166] This may in fact be mediated by mTORC1, which is activated upon AMPK inhibition. mTORC1 increases HIF1α levels,[95,96] which in turn can activate the expression of almost all glycolytic enzymes.[167]

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 on the other hand autophagy seems to promote stress survival in established tumors (reviewed by Yang et al.[168]). There are 3 different types of autophagy (reviewed in Boya et al.[169] and Marino et al.[170]): macroautophagy, microautophagy, and chaperon-mediated autophagy (CMA). Macroautophagy, hereafter called autophagy, is divided into 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), and FAK family kinase-interacting protein of 200 kDa (FIP200).[171,172] mTORC1 and AMPK phosphorylate ULK1 on different sites and thereby respectively inhibit or activate autophagy.[173] mTORC1 phosphorylates ULK1[173] and ATG13,[172] reducing ULK1 complex stability and ULK1 kinase activity.[174,175] In contrast, AMPK binds to the mTORC1-bound ULK1 complex and phosphorylates raptor[176] and ULK1[173] to activate autophagy. Another modulator of autophagy initiation is the Bcl-2/Beclin 1 complex, which inhibits phagophore maturation.[177] 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,[178,179] disrupting its binding to Beclin 1 and inducing autophagy. ER stress also induces autophagy when inhibiting the PI3K–Akt pathway[180] and mTORC1.[181] Both ER stress and hypoxia induce ATF4, which directly upregulates ULK1 transcription and ULK1 complex activity.[182,183] In addition, ATF4 induces TRB3 expression[89,184] resulting in inhibition of Akt, which may potentially induce autophagy via mTORC1 inhibition. Furthermore, hypoxia induces autophagy by activating AMPK[185] and BNIP3/BNIP3L,[186–188] 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.[189] In addition, oxidative stress also activates CMA,[190] a process in which proteins are unfolded and directly trans-localized through the lysosomal membrane.

In cancer cells, autophagy is necessary to maintain the 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, inactivation of the negative AMPK regulator FLCN leads to stress resistance via autophagy induction.[191] Furthermore, autophagy inhibition correlates with induction of apoptosis during cancer-related hypoxia and thus seems to have an important function in tumor cell survival under endogenous stress.[192] In addition, autophagy induction often correlates with cancer resistance to chemotherapeutics.[193,194] In contrast, prolonged autophagy induction has been suggested to result in cell death (reviewed by Loos et al.[195] and Marino et al.[170]). 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.
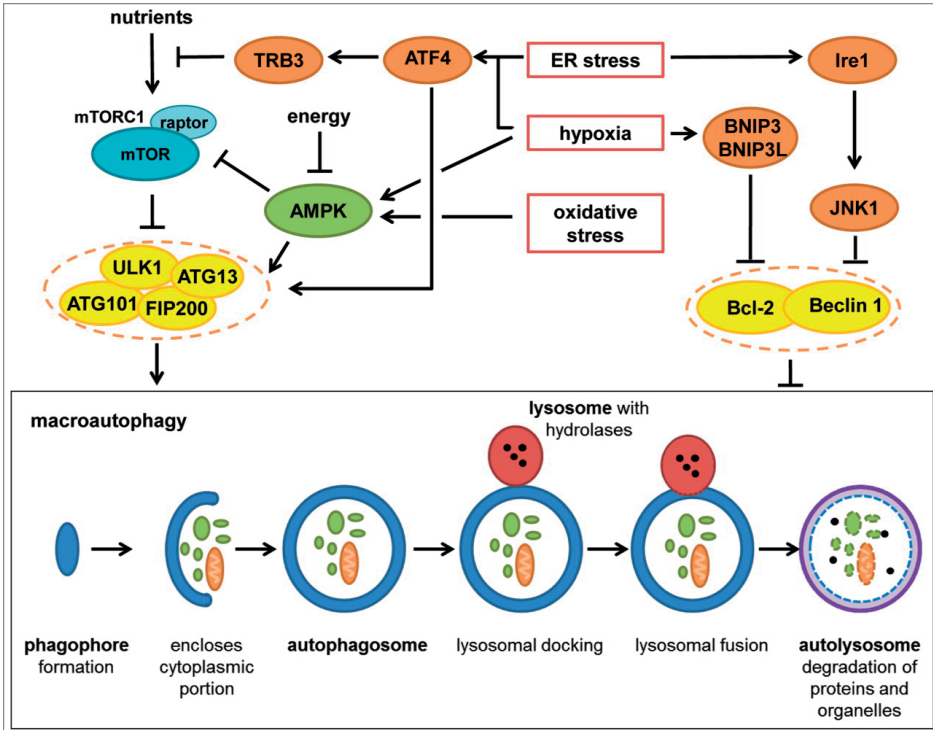
Figure 3. Autophagy regulation by stress. The ULK1 complex (ULK1, ATG13, ATG101, and FIP200) and the Bcl-2–Beclin 1 complex are major autophagy regulators. Autophagy can be divided into 3 different steps: (1) phagophore formation and enlargement (autophagosome); (2) lysosomal docking and fusion with the autophagosome (autolysosome); (3) degradation of proteins and organelles in the autolysosome. The ULK1 complex is needed for autophagy initiation, whereas assemble of the Bcl-2–Beclin 1 complex 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 transcription of stress factors such as 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 disassembly of the Bcl-2–Beclin 1 complex. 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.

BALANCING MTORC1 UNDER STRESS: STRESS GRANULES AS GUARDIANS OF CANCER CELLS?

mTORC1 activity contributes to many aspects of 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 those 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. Stress granules (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.[196–198] 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 2α (eIF2α) kinases (reviewed by Donnelly et al.[199]), which phosphorylate eIF2α at serine 51. eIF2α is a subunit of eIF2, which together with t-RNA[fMet] and GTP forms a ternary complex that is required for formation of the 48S translation preinitiation complex. Phosphorylation of eIF2α prevents ternary complex formation, leading to polysome disassembly and producing a non-canonical 48S* complex that is unable to recruit the 60S ribosomal subunit. In mammals, 4 eIF2α kinases have been described: hemin-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,[200] ER stress,[201] and amino acid starvation.[202] Polysome disassembly changes the fate of many proteins involved in mRNA processing, leading to accumulation of mRNAs that disassemble from polysomes. The morphological consequence of this process is the formation of cytoplasmic SGs, which are protein–RNA assemblies.[203] SGs have an antiapoptotic function under stress,[131,204] and their formation after chemotherapy or radiotherapy in cancer correlates with therapy resistance.[205,206] Thus, SGs could help the tumor to balance stress signaling and 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*.[207,208] Thus, overexpression of nucleators *in vivo* has the potential to promote SG formation in cancer cells. Examples of nucleators are Ras-GTPase activating protein SH-3 domain binding protein 1 and 2 (G3BP),[207,209] T cell intracellular antigen (TIA-1) and TIA-1–related protein (TIAR),[210,211] polyadenylate-binding protein 1 (PABP1),[208] and fragile X mental retardation protein (FMRP).[212] Protein levels of SG nucleation factors are induced in several tumor entities.[213–215] For example, French et al.[213] analyzed 22 breast cancer samples, all of which showed elevated G3BP1. After the nucleation and aggregation phases, further proteins that have intrinsic mRNA binding capacity or that bind to SG proteins by piggy back recruitment, are assembled into SGs.[216] Upon stress relief, SGs dissolve and SG proteins relocate to their previous compartments.[197,208,217] SGs are thought of as sites of RNA storage and triage

during stress.[218] In addition, there is increasing evidence that SGs interfere with stress signaling pathways (reviewed by Kedersha et al.[216]). Proteins involved in apoptosis can be recruited to SGs, which thereby promote survival. For example, SG recruitment of signaling scaffold protein receptor of activated protein kinase C 1 (RACK1) prevents induction of apoptosis by the genotoxic stress-activated p38 and JNK–MAPK pathways[204], and ubiquitin-specific protease 10 (USP10) has been reported to exert an antioxidant apoptosis-preventing activity that depends on recruitment of USP10 to SGs.[219] Recruitment of TNF receptor-associated factor 2 (TRAF2) to SGs inhibits proinflammatory tumor necrosis factor α (TNFα)–NF-κB signaling.[220]

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).[131,208,217] In cancer cells, DYRK3 integrates mTORC1 activity with SG formation via a dual mechanism.[217] During prolonged stress, DYRK3 is sequestered into SGs where it prevents SG dissolution and mTORC1 release. After stress release, DYRK3 phosphorylates and inhibits the mTORC1-inhibitor PRAS40,[221–227] thus contributing to mTORC1 reactivation. Furthermore, the adaptor protein astrin disassembles mTORC1 by sequestering raptor into SGs.[131] Through this recruitment SGs restrict mTORC1 assembly and prevent its hyperactivation and mTORC1-dependent oxidative stress-induced apoptosis. Thus, inhibition of astrin induces mTORC1-triggered apoptosis in cancer cells.[131] 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.[228, 229] 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 reactivation after stress correlates with its release from SGs.[208] 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;[206] for example, formation of 5′cap–eIF4F complexes requires phosphorylation of 4EBP1 by mTORC1.[230] Thus, SGs and mTORC1 are connected via a NFL in which mTORC1 positively regulates SGs, whereas SGs inhibit mTORC1 (**Fig. 4**).
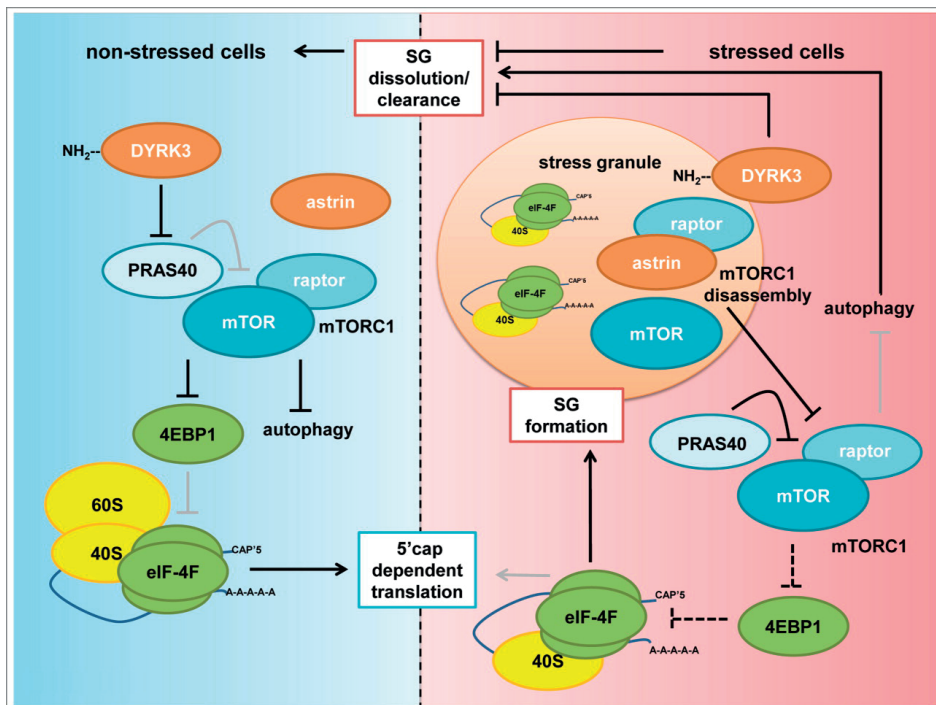
Figure 4. Stress granules and mTORC1. Under non-stressed conditions DYRK3 phosphorylates and inactivates the mTORC1 inhibitor PRAS40. Active mTORC1 inhibits 4E-BP1, allowing for eIF4F–5′cap–mRNA complex formation, ribosomal binding, and translation initiation. Stressed conditions induce translational arrest, polysome disassembly, and SG formation. mTORC1 is disassembled, and the mTORC1 components mTOR and raptor are recruited to SGs. Kinase-inactive DYRK3 localizes through its N-terminus to SGs, 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 induction of autophagy, which is required for SG clearance after stress release and for SG formation. However, inhibition of 4E-BP1 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, gray arrows represent inactive connections in stressed versus non-stressed cells.

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.[231] However, in a background of mTORC1 inhibition and reduced overall translation levels, stress

response proteins still need to be expressed[232] although active translation requires mTORC1 activity. Thus, there is a seemingly contradictory requirement for mTORC1 activation/inhibition during stress. SGs have emerged as excellent candidates for balancing mTORC1 activity and the dependent translational events. Both mTORC1 and SGs control translation of stress related factors,[29,34,233–235] and SGs have been suggested as sites of stress-specific translation initiation.[236] Translation under stress depends on upstream open reading frames (uORFs) and internal ribosomal entry sites (IRES).[218,237–239] mTORC1 induces both IRES-mediated[240,241] and uORF-dependent translation via eIF4GI,[242] 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 kDa heat shock protein (Hsp70) require mTORC1 for their expression under oxidative stress.[131] hnRNP-A1 is required for IRES-mediated translation under stress in tumor cells,[243,244] whereas HSF1 mediates transcriptional events under stress, including Hsp70 expression.[233] Additionally, ATF4 protein expression under stress is regulated by mTORC1.[131] The ATF4 mRNA contains 2 uORFs, leading to increased ATF4 translation in response to stress-related eIF2α phosphorylation.[239] ATF4 induces autophagy under ER stress and hypoxia (see above). Of note, autophagy is required for SG clearance in yeast and mammalian cells,[245,246] and inhibition of autophagy results in mistargeting of proteins to SGs.[246] Thus, it seems that, while mTORC1 must 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 that balances mTORC1 activity under stress.

THERAPEUTIC IMPLICATIONS: MTORC1 IN STRESS AS A TARGET IN CANCER?

mTORC1 signaling is mostly perceived as a prosurvival and antiapoptotic process. However, there is ample evidence that dysregulated hyperactive signaling via mTORC1, for example 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 the induction of cell death 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, in 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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