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CELL SCIENCE AT A GLANCE

The flipside of the TOR coin – TORC2 and plasma membrane homeostasis at a glance

Margot Riggi[1,2,3], Beata Kusmider[1,3] and Robbie Loewith[1,3,*]

ABSTRACT

Target of rapamycin (TOR) is a serine/threonine protein kinase conserved in most eukaryote organisms. TOR assembles into two multiprotein complexes (TORC1 and TORC2), which function as regulators of cellular growth and homeostasis by serving as direct transducers of extracellular biotic and abiotic signals, and, through their participation in intrinsic feedback loops, respectively. TORC1, the better-studied complex, is mainly involved in cell volume homeostasis through regulating accumulation of proteins and other macromolecules, while the functions of the lesser-studied TORC2 are only now starting to emerge. In this Cell Science at a Glance article and accompanying poster, we aim to highlight recent advances in our understanding of TORC2 signalling, particularly those derived from studies in yeast wherein TORC2 has emerged as a major regulator of cell surface homeostasis.

KEY WORDS: TORC2, Membrane tension homeostasis, Protein kinase, Signalling

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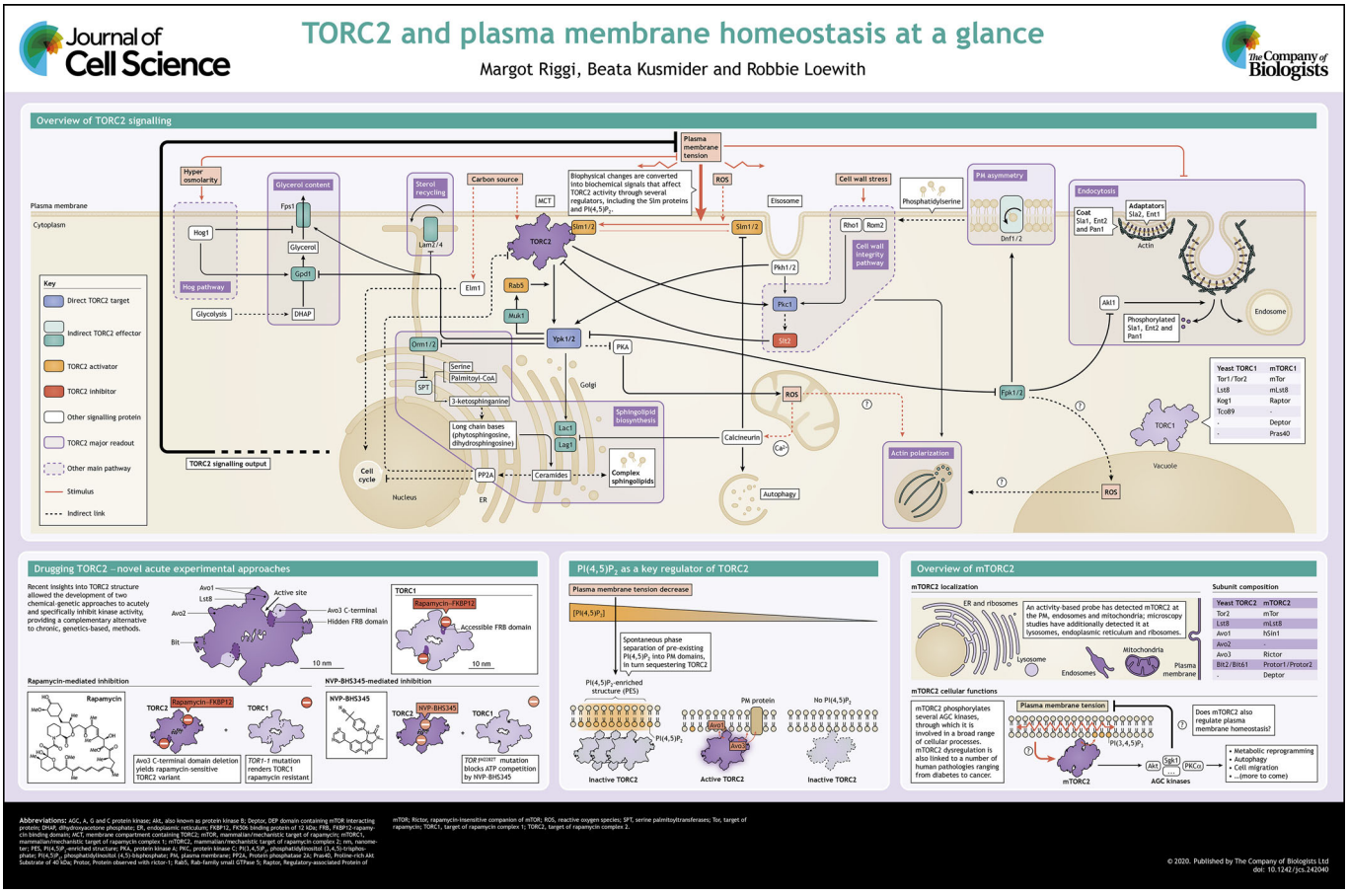
Introduction

Constant change of the environment is a threat to the maintenance of metabolic homeostasis and requires all organisms to adapt in order to survive and prosper. To these ends, organisms have evolved finely tuned regulatory mechanisms allowing for growth in favourable conditions, while enabling survival and restraint of anabolic processes upon stressful conditions. In eukaryotes, much of this regulation relies on the large target of rapamycin (TOR) protein kinase. TOR assembles into two, highly conserved,



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multiprotein TOR complexes known as TORC1 and TORC2 (Loewith et al., 2002; Kim et al., 2002; Hara et al., 2002; Wedaman et al., 2003; Jacinto et al., 2004; Sarbassov et al., 2004; Van Dam et al., 2011; Tatebe and Shiozaki, 2017). These complexes are broadly considered to be major regulators of cellular growth and serve as direct transducers of extracellular biotic and abiotic signals. In addition to this traditional view, there is growing evidence that these complexes also act in feedback loops to mediate various aspects of cellular and organismal homeostasis (Eltschinger and Loewith, 2016). In accordance with this central function, mammalian TOR (mTOR, also known as mechanistic target of rapamycin) is implicated in an increasing number of different human diseases, and has been a validated drug target since the macrolide rapamycin was first approved as an immunosuppressant more than 20 years ago (Liko and Hall, 2015). Given their central role in growth regulation, in addition to their clinical relevance, studies aimed at understanding how the TOR complexes are themselves regulated and the plethora of growth-related processes they control, have been, and continue to be, of high priority.

Despite sharing general architectural features, TORC1 and TORC2 are spatially and functionally distinct (Eltschinger and Loewith, 2016; Loewith and Hall, 2011; Loewith et al., 2002; Wedaman et al., 2003). In yeast, TORC1, which localizes to vacuolar and/or endosomal membranes (Hatakeyama and De Virgilio, 2019; Berchtold and Walther, 2009; Sturgill et al., 2008), contains two copies of either Tor1 or Tor2 (orthologues of the single mTOR in mammals) and additionally two copies each of lethal with Sec13 number 8 (Lst8; mLst8 in mammals), kontroller of growth 1 (Kog1; Raptor in mammals) and TOR complex one protein of 89 kDa (Tco89; no reported mammalian orthologue). In contrast, TORC2 localizes to puncta at the plasma membrane (Berchtold and Walther, 2009). This complex is built exclusively on a dimer of Tor2 together with two copies each of Lst8, adheres voraciously to Tor2 number 1 (Avo1; mSin1, also known as MAPKAP1, in mammals), Avo2 (no reported mammalian orthologue), Avo3 (Rictor in mammals) and binding partner of Tor2 of 61 kDa (Bit61) and/or its paralog Bit2 (Protor1 or Protor2, also known as PRR5 and PRR5L, in mammals; see poster).

The Tor1 or Tor2 subunit in TORC1, as well as mTOR in mTORC1, can be bound by rapamycin, resulting in a loss of phosphorylation of TORC1 (mTORC1) substrates. In contrast, Tor2 (mTOR) in TORC2 (mTORC2) cannot be bound by rapamycin and the activities of these complexes are therefore unaffected by acute rapamycin treatment. Correspondingly, rapamycin has been instrumental in the dissection of TORC1 (mTORC1) signalling, whereas the lack of an equivalent inhibitor has considerably hampered the characterization of TORC2 (mTORC2) signalling. To remedy this, chemical-genetic approaches that enable the acute and specific inhibition of TORC2 in the model eukaryote *Saccharomyces cerevisiae* have recently been developed – the fruits of some of these labours are presented below.

Rather than mapping an exhaustive network of TORC2-related pathways as recently detailed elsewhere (Roelants et al., 2017), this Cell Science at a Glance article and accompanying poster aim to highlight novel key concepts in the field, particularly those derived from studies in yeast wherein TORC2 has emerged as a major regulator of plasma membrane (PM) homeostasis. In this regard, this short review complements a recent Cell Science at a Glance article on ‘Nutrient regulation of mTORC1 at a glance’ (Condon and Sabatini, 2019).

TORC2 structure

Low-resolution (Gaubitz et al., 2015) and moderate-resolution structures of yeast and mammalian TORC2 (Karuppasamy et al., 2017; Stuttfeld et al., 2018; Chen et al., 2018) have been published in the past few years, providing insights into the function of its various subunits. Comparison with TORC1 structures (Aylett et al., 2016; Yang et al., 2016; 2017; Chao and Avruch, 2019) (see poster), shows that the two complexes share a common architecture of a 3D rhombohedron that is nucleated around a Tor–Lst8 core dimer that delineates a central cavity of unknown function. This cavity is much larger in mTORC1 compared to mTORC2. Avo3 (Rictor), the TORC2-defining subunit, binds to the HEAT repeats in TOR that are also involved in TOR dimerization. Kog1 (Raptor), the TORC1-defining subunit occupies the same space in mTORC1, explaining the mutual exclusivity of these two proteins in their respective TOR complex (Karuppasamy et al., 2017; Chen et al., 2018; Stuttfeld et al., 2018). Avo3 has an important scaffolding function since its depletion triggers the disassembly of TORC2 (Wullschleger et al., 2005). It also contributes to the PM localization of TORC2 (Martinez Marshall et al., 2019). Avo1 possesses a PH domain that is able to bind various phosphoinositides and has been reported to tether TORC2 to the PM (Berchtold and Walther, 2009). The conserved-region-in-the-middle (CRIM) domain of Avo1, although mobile, and thus poorly resolved in EM images, can be extensively cross-linked to Lst8 in chemical crosslinking experiments (Gaubitz et al., 2015), positioning it in proximity to the TORC2 active site cleft (Karuppasamy et al., 2017). These unique features are consistent with a role for Avo1 in coupling an appropriate PM localization to substrate recruitment and signalling output of the complex. Higher-resolution TORC2 structures are desired as these would help elucidate the functions of the enigmatic Bit61 and Bit2 (Protor) subunits and potentially the various orientations of Avo1/mSin1. Nevertheless, the current structures have been informative, not only to visualize overall architecture but also to design of TORC2 inhibitors.

Chemical-genetic tools to acutely inhibit TORC2 signalling

Upon its cell entry, rapamycin first forms a complex with the proline isomerase FKBP12 (also known as Fpr1) and subsequently engages with the FKBP12-rapamycin binding (FRB) domain of Tor; this inhibits downstream signalling by restricting access of substrate to the active sites (Yang et al., 2013). Missense mutation leading to an amino acid substitution in the FRB domain (e.g. in the *TOR1-1* allele in which Ser1972 is changed to Arg), prevents rapamycin binding and confers dominant resistance to the drug (Kunz et al., 1993; Helliwell et al., 1994; Heitman et al., 1991; Cafferkey et al., 1993). In TORC2, a density attributed to Avo3 occludes the FRB domain of Tor2, explaining why this complex is insensitive to rapamycin (Gaubitz et al., 2015; Karuppasamy et al., 2017). Strikingly, C-terminal truncation of Avo3 yields a TORC2 variant that is sensitive to rapamycin. Combining this Avo3 truncation with the rapamycin-resistant *TOR1-1* allele yields a yeast strain in which only TORC2 activity is acutely inhibited by rapamycin (Gaubitz et al., 2015). Alternatively, but still exploiting the fact that Tor1 can nucleate only TORC1 and not TORC2, in yeast cells expressing Tor1 with an amino acid substitution in the ATP-binding pocket of Tor1, Met2282 to Thr, binding of ATP-competitive inhibitors, such as NVP-BHS345 or CMB4563, is prevented, allowing for the specific inhibition of TORC2 with these molecules (Rispal et al., 2015; Bourgoint et al., 2018). These orthogonal approaches to specifically and acutely inhibit TORC2 promise to be useful tools to further characterize TORC2 signalling in yeast.

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TORC2 is a key regulator of PM tension

The punctate nanodomains in which TORC2 resides are called plasma membrane compartments containing TORC2 (MCTs; Berchtold and Walther, 2009). Coherent with its subcellular localization, and as comprehensively reviewed recently (Roelants et al., 2017), TORC2, through activation of its main substrates, the protein kinase A, G and C (AGC)-family kinase Ypk1 and its paralog Ypk2 (Kamada et al., 2005; Niles and Powers, 2012; Leskoske et al., 2017), regulates a growing list of downstream effectors, the ensemble of which control virtually every aspect of PM homeostasis. This list includes processes such as sphingolipid biosynthesis (Aronova et al., 2008; Beeler et al., 1998; Muir et al., 2014; Roelants et al., 2011) sterol recycling (Roelants et al., 2017), membrane trafficking – of which endocytosis is the best characterized (Alvaro et al., 2016; Roelants et al., 2017; Bourgoint et al., 2018; Riggi et al., 2019), PM bilayer asymmetry (Roelants et al., 2010) and osmoregulation (Lee et al., 2012; Muir et al., 2015) (see poster; Roelants et al., 2017). Collectively, these distal effectors of TORC2 contribute to the maintenance of a particular property of the PM, its line tension.

Concrete evidence for TORC2-mediated regulation of PM tension was recently enabled through the development of a novel mechanosensitive probe, named Flipper-TR® (Riggi et al., 2018). Flipper-TR® is a lipophilic small-molecule that intercalates into the PM of living cells where its fluorescent lifetime reports on relative changes in PM tension (Colom et al., 2018). Using this probe, we demonstrated that specific inhibition of TORC2 through the rapamycin-based chemical-genetic approach described above leads to a dramatic increase in PM tension, whereas hyperactivation of downstream signalling, in cells expressing a hyperactive allele of *YPK1*, results in constitutively low membrane tension (Riggi et al., 2018). PM tension homeostasis is incredibly important for all eukaryote cells, with the most obvious example of this importance being cell lysis if tension becomes too high. However, appropriate tension must also be maintained for other reasons. For instance, too much tension will block membrane-deforming events such as endocytosis (Riggi et al., 2019), whereas too little tension will not only impact membrane trafficking, but also all the enzymatic and signalling activities of the plethora of membrane-associated proteins that require defined membrane properties for their optimal function. The conservation of such a role of mTORC2 in membrane tension homeostasis in larger eukaryotes is anticipated, but has not yet been explicitly demonstrated (see below).

The role of TORC2 in PM tension homeostasis was not initially obvious. The first described output of TORC2 signalling was the cell-cycle-dependent polarization of the actin cytoskeleton, which directs the secretory apparatus towards the bud (Schmidt et al., 1996), thus enabling its increase in mass, volume and surface area. TORC2 is linked to the actin cytoskeleton through multiple crosstalks with the cell wall integrity (CWI) MAPK pathway, both directly as TORC2 phosphorylates the sole protein kinase C (PKC) orthologue in yeast, Pkc1 (Levin et al., 1990; Nomura and Inoue, 2015), and, indirectly through the Ypk1-mediated inhibition of the flippase kinase paralogs (Fpk1 and Fpk2) and the downstream aminophospholipid flippase-dependent control of phosphatidylserine distribution at the PM (Roelants et al., 2010). In turn, this influences the localization and activity of the small GTPase Rho1 and/or of its guanine-nucleotide exchange factor (GEF) Rom2 (Hatakeyama et al., 2017). This signalling is bidirectional, as Slt2, the MAPK of the CWI pathway, can reciprocally phosphorylate the Avo2 subunit of TORC2, resulting in TORC2 inhibition (Leskoske et al., 2018) (see poster).

Generally speaking, it is becoming more and more difficult to envision TORC2 signalling independently of the global cellular signalling landscape. Indeed, a co-requisite for TORC2-mediated activation of Ypk1 is the phosphorylation of its activation loop by one of the Pkh paralogs, Pkh1 or Pkh2 (Roelants et al., 2002). As these kinases are regulated by ceramides (Friant et al., 2001; Luo et al., 2008), this constitutes an additional entry point for sphingolipid-derived signals into TORC2 downstream signalling (see poster). Such an intricate network of connected and partially redundant pathways ensures an efficient and coordinated cellular response to changes in both environmental and internal conditions; but, what are the molecular events that directly regulate TORC2?

TORC2 is itself regulated by PM tension

It has recently become clear that TORC2 activity not only regulates PM tension, but is itself acutely regulated by PM tension; increased tension – confirmed with the Flipper-TR® probe – activates TORC2, while decreased tension leads to TORC2 inhibition (Berchtold et al., 2012; Riggi et al., 2018). This demonstrates that TORC2 guards against changes in PM tension by operating in a homeostatic feedback loop. But how are biophysical changes in membrane tension converted into biochemical signals that regulate TORC2? Part of the answer to this question may be found in the several direct TORC2 regulators that have been proposed in recent years and which are discussed below. These include the BAR- and PH-domain-containing paralogs Slm1 and Slm2 (Audhya et al., 2004), the phosphoinositide phosphatidylinositol (4,5)-bisphosphate [$PI(4,5)P_2$] and reactive oxygen species (ROS), as well as several different small GTPases (Saci et al., 2011; Hatano et al., 2015; Senoo et al., 2019; Locke and Thorner, 2019b).

Slm1 and Slm2

During exponential growth, Slm1 and Slm2 are approximately equally partitioned between MCTs and invaginated domains of the PM called eisosomes. An acute increase in PM tension, triggered by various orthogonal approaches, such as hypotonic shock, blockage of sphingolipid biosynthesis or physical pulling of the PM, triggers a delocalization of Slm1 and/or Slm2 from eisosomes and an activation of TORC2 signalling, albeit through a still poorly characterized mechanism (Berchtold et al., 2012) (see poster). A role for the Slm proteins in TORC2 function, and in particular in Ypk1 recruitment to the PM, has also been independently reported by others (Niles and Powers, 2012). Eisosomes may represent a fungal equivalent to caveolae, analogous PM invaginations in mammalian cells, which have been postulated to function as tension-sensitive membrane reservoirs (Simunovic et al., 2015; Parton, 2018; Zahumensky and Malinsky, 2019). The putative F-BAR domain of Slm1 and/or Slm2 may sense membrane curvature at the eisosome, which would be diminished or lost upon increased tension of the PM; this could potentially trigger the dissociation of Slm1 and/or Slm2 from eisosomes and their subsequent accumulation in MCTs and activation of TORC2. Although unproven, this model has some support from studies in *Schizosaccharomyces pombe* spheroplasts, where eisosome-associated Pil1 clusters have been observed to disassemble upon hypo-osmotic shock (Kabeche et al., 2015).

$PI(4,5)P_2$

Surprisingly, loss of membrane tension can also be sensed through a different mechanism that is independent of Slm1 and/or Slm2 (Riggi et al., 2018). Acute loss of membrane tension that is triggered by hypertonic shock or treatment with palmitoylcarnitine, a human

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metabolite (absent from yeast), which integrates into the yeast PM, causes a spontaneous phase separation of pre-existing $PI(4,5)P_2$ into domains that sequester and inactivate TORC2 (Riggi et al., 2018) (see poster). Why TORC2 that is sequestered into these $PI(4,5)P_2$-enriched domains is inactive remains to be determined, but this could be related to the inactive polymer TORC1 has been shown to form upon nutrient depletion (Prouteau et al., 2017). It is important to note that $PI(4,5)P_2$ is thus both necessary for TORC2 localization to the PM (Berchtold and Walther, 2009) as well as for its inactivation in response to a drop in PM tension (Riggi et al., 2018).

Based on the observation that deletion of the PH domain of Avo1 is lethal, but can be rescued by its replacement with another PM-targeting domain (the CAAX box), Avo1 has been generally assumed to mediate the anchoring of TORC2 to the PM though an interaction with $PI(4,5)P_2$ (Berchtold and Walther, 2009). However, a recent study proposes a different model, in which the N-terminal armadillo repeats of Avo3 anchor TORC2 to the PM independently of $PI(4,5)P_2$, either through a direct interaction with negatively charged head groups of PM phospholipids, or indirectly through a yet unidentified PM protein (Martinez-Marshall et al., 2019). This work confirmed the importance of $PI(4,5)P_2$ for TORC2 activity, possibly through eisosome formation and/or the recruitment of Slm1 and/or Slm2 to the PM (Martinez-Mashall et al., 2019). Alternatively, $PI(4,5)P_2$ could act as a positive allosteric activator by alleviating a potential occlusion of the active site of Tor2 by the PH domain of Avo1 (Liu et al., 2015; Yuan and Guan, 2015). In contrast, as noted above, a local accumulation of $PI(4,5)P_2$, which occurs upon a decrease in PM tension, has been shown to correlate with TORC2 inhibition (Riggi et al., 2018). Although details remain to be clarified, these results suggest a new role for $PI(4,5)P_2$ as an allosteric regulator of TORC2, thereby integrating various cues at the PM and acting either in a positive or negative manner, depending on the global input. This is intriguing in light of the fact that TOR itself is the founding member of the atypical phosphatidylinositol kinase related kinases (PIKKs) family, protein kinases that possess a curious resemblance to lipid kinases (Keith and Schreiber, 1995). Perhaps, during evolution, PIKKs stopped using phosphoinositides as substrates and instead began to use them as allosteric regulators.

Collectively, the studies demonstrating that TORC2 functions in a feedback loop to maintain PM tension homeostasis call to attention a broader, often underexplored issue, that is, the importance of physical cues in cell signalling. The discovery of the mode-of-action of palmitoylcarnitine, which induces a decrease in PM tension through intercalation within the bilayer, further suggests that the PM, and perhaps other membranes as well, may be targeted by small molecules for therapeutic gain (Loewith et al., 2019).

ROS

As is the case for PM tension, TORC2 may also function in a feedback loop to regulate redox homeostasis. TORC2, via Ypk1, regulates the generation of ROS through two effector branches, which, respectively, lead to the vacuole via Fpk1 and Fpk2, and mitochondria via protein kinase A (PKA) (Niles et al., 2014) (see poster). In turn, ROS levels appear to regulate the localization of Slm1 and Slm2 and, consequently, TORC2 activity (Niles et al., 2014; Niles and Powers, 2014). Tracking the targets of ROS signalling is notoriously difficult, but some progress has been made. For example, TORC2-mediated regulation of mitochondrial oxidative stress modulates calcineurin activity through the Ca^{2+} channel regulatory protein Mid1 (Vlahakis et al., 2016). Calcineurin, in turn, counters TORC2 signalling (see poster) by dephosphorylating the Ypk1-mediated phosphorylation of the ceramide synthase enzymes Lac1 and Lag1 (Aronova et al., 2008) and by dephosphorylating Slm1 and Slm2 (Bultynck et al., 2006; Mulet et al., 2006; Tabuchi et al., 2006). TORC2-mediated maintenance of redox homeostasis, and its potential conservation in larger eukaryotes, are intriguing topics for future studies.

Glucose and GTPases

Nutrient signalling to TORC1 is now well established, and recent studies suggest that TORC2 signalling is also responsive to nutrients, in particular glucose. Indeed, cells compromised in TORC2 signalling cannot properly couple their growth rate to nutrient availability (Lucena et al., 2018). Probing this phenomenon, the Kellogg group has described roles for Elm1, the yeast homolog of the Lkb1 tumour suppressor kinase (also known as STK11), and type 2A protein phosphatases in coupling carbon-source cues to TORC2 activity (Alcaide-Gavilán et al., 2018). Although the molecular details remain to be discerned, this signalling pathway appears to provide a mechanism to link growth rate to membrane expansion and cell size.

TORC2 activity in the fission yeast *S. pombe* also appears to be regulated by glucose-derived signals (Hatano et al., 2015). In this case, glucose signalling to TORC2 is mediated by the Rab family GTPase Rhy1. In the presence of glucose, Rhy1 is loaded with GTP and binds to TORC2, which enhances TORC2-mediated phosphorylation of the Ypk1 ortholog Gad8 (Hatano et al., 2015). Subsequently, Rab5 in budding yeast was also found to activate TORC2, curiously, as part of a feed-forward pathway for sustained upregulation of TORC2–Ypk1 signalling (Locke and Thorner, 2019a). Specifically, Ypk1 phosphorylates and activates Muk1, one of the two GEFs for Rab5, which in turn acts as an activator of TORC2 (see poster). In this work, an elegant model is suggested, in which Ypk1 acts as a coincidence detector to localize a maximal activity of TORC2 in close vicinity to early endosomes, both sensing and modulating the rate of vesicle trafficking (Locke and Thorner, 2019a).

How Rab5 GTPases activate TORC2 will be an important question for future studies. Interestingly, Rab5 is not the only GTPase that interacts with TORC2. The *Dictyostelium discoideum* Avo1 ortholog, RIP3, was first discovered as a Ras-interacting protein (Lee et al., 1999), and the interaction of Ras-GTP with TORC2 is important for chemoattractant-induced cell migration (Lee et al., 2005; Senoo et al., 2019). Ras has also been found to activate TORC2 in mammals and this activation contributes to Ras-dependent neoplasia (Kovalski et al., 2019). Finally, Rac1 has also been reported to control cell growth by regulating the activities of both mTORC1 and mTORC2 (Saci et al., 2011). Indeed, given the well-documented regulation of mTORC1 by Rag and Rheb GTPases (Durán and Hall, 2012), it perhaps should not come as a surprise that TORC2 is similarly regulated by multiple GTPases.

And in metazoans?

TOR signalling is robustly conserved from yeast to humans; however, our knowledge of mTORC2 still presents some gaps. In particular, the subcellular localization of mTORC2 is heavily debated – it has been reported to localize to the PM, lysosomes, ER, mitochondria, ER–mitochondria membrane junctions and ribosomes (Betz and Hall, 2013; Arias et al., 2015; Zinzalla et al., 2011; Boulbés et al., 2011; Liu et al., 2015). An activity-based probe recently located active mTORC2 at the PM, and to a lesser extent at mitochondria and a subset of endosomes (Ebner et al., 2017). Not taking into account technical limitations, differences

between cell types or responses to various upstream cues could at least partially account for the reported discrepancies.

A localization of mTORC2 to the PM would be consistent with a conserved role in the maintenance of PM homeostasis, and indeed, some data support the idea that mTORC2 activity is regulated by PM tension (Kippenberger et al., 2005). Membrane stretch has been reported to trigger mTORC2-dependent phosphorylation of Akt, and, in striking resemblance to the role played by eisosomes in yeast, stretch-mediated activation was shown to involve caveolae (Sedding et al., 2005; Zhang et al., 2007). PM tension has additionally been shown to act through phospholipase D2 (PLD2) and mTORC2 to limit actin network assembly during neutrophil migration (Diz-Muñoz et al., 2016). Collectively, these observations support the notion that mTORC2, like yeast TORC2, plays a role in PM homeostasis, a hypothesis to be confirmed or refuted through future studies.

Conclusions and perspectives

Classically, mTORC2 is thought to function primarily as an effector of phosphoinositide 3-kinase (PI3K) signalling, which is activated by growth factors such as insulin (Sarbassov et al., 2005; Guertin et al., 2006). However, such signalling pathways are absent in lower eukaryotes, suggesting that TORC2 possesses a more primordial function. From recent work in yeast elaborated above, we would argue that this function would be to maintain PM homeostasis.

Genetic studies have implicated mTORC2 in a number of human pathologies, ranging from diabetes to cancer (Liu and Sabatini, 2020), for example, as a Ras effector, as mentioned above (Kovalski et al., 2019). Consequently, finding drugs to inhibit or modulate mTORC2 activity is of major interest. Interestingly, a molecule that blocks the incorporation of Rictor into mTORC2 was recently identified and this drug was shown to have potential in pre-clinical glioblastoma models (Benavides-Serrato et al., 2017). It will be exciting to see if this molecule, or derivatives thereof, live up to this initial promise. Alternatively, our work with palmitoylcarnitine suggests that small molecules may be developed to target the biophysical properties of the PM as a means to modulate mTORC2 activity for therapeutic gain (Loewith et al., 2019). It should be noted, however, that some studies have suggested that mTORC2 inhibition may present undesired consequences. For example, chronic treatment with rapamycin, which ultimately prevents assembly of nascent mTOR into mTORC2, was associated with impaired glucose tolerance in mice due to loss of mTORC2 activity (Lamming et al., 2012, 2014). Clearly, more needs to be learned about mTORC2 signalling before attempts are made to target it for therapeutic gain.

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Competing interests

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Cell science at a glance

A high-resolution version of the poster and individual poster panels are available for downloading at http://jcs.biologists.org/lookup/doi/10.1242/jcs.242040.supplemental

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