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Folliculin – a tumour suppressor at the intersection of metabolic signaling and membrane traffic

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Abstract

The Birt-Hoge-Dubé syndrome tumour suppressor Folliculin is a regulator of metabolism and has as a wide range of cellular and organismal phenotypes associated with its disruption. However, the molecular mechanisms which underlie its functions are poorly understood. Folliculin has been described to associate with lysosomes in response to nutrient depletion and form a key part of the signaling network that controls the activity of mTORC1. We recently reported that Folliculin can control the nutrient dependent cytoplasmic distribution of lysosomes by promoting the formation of a complex with the Golgi-associated small GTPase Rab34 and its effector RILP. We thus define a mechanistic connection between the lysosomal nutrient signaling network and the transport machinery that controls the distribution and dynamics of this organelle. Here we summarise the main conclusions from that study, attempt to integrate our findings with other recent studies on lysosome distribution/dynamics, and discuss the potential consequences of the dysregulation of this processes caused by Folliculin loss for Birt-Hoge-Dubé syndrome and normal cell function.

The tumour suppressor Folliculin (*FLCN*) is disrupted in the autosomal dominant Birt-Hoge-Dubé (BHD) syndrome. BHD syndrome patients may present with lung cysts that can cause spontaneous pneumothorax, skin tumours known as fibrofolliculomas as well as kidney cysts and kidney cancer [1]. It has been clear for some time that the 64kDa protein product of the *FLCN* gene is a regulator of cellular metabolism that is expressed in most cell types [2]. FLCN can form a complex with two larger (≈ 125-130kDa) proteins FNIP1 and FNIP2 (***F**olliculin **I**nteracting **P**roteins* 1 and 2) [2,3]. Lst7 and Lst4 form an orthologous complex in yeast [4,5]. Recent structural studies have shown that FLCN and FNIP proteins are both comprised of a Longin and a DENN domain – both of which are protein folds that have been variously implicated in the regulation of small GTPases and membrane traffic [6-8].

Both on an organismal and cellular level, *FLCN* is pleiotropic, and many phenotypes appear to be highly context dependent. For example, FLCN has been proposed to both positively and negatively regulate cell-cell adhesion and migration [9-11], and BHD renal tumors may have either increased or decreased mTORC1 activity [12,13]. The FLCN/FNIP complex interacts with AMPK and dependent on the system studied appears to either promote, suppress or have little effect on its activity [2,14,15]. FLCN/FNIP have also been linked to diverse cell functions such as autophagy [16,17], ciliogenesis [18], exit of stem cells from pluripotency [19] and lysosome biogenesis [20,21]. Together, these data point to a central role for FLCN/FNIP in metabolic homeostatsis, but also show that loss or disruption of FLCN impacts on a range of cellular functions.

On a mechanistic level, recent studies from the Sabatini and Ferguson groups have provided a particularly crucial insight; FLCN (which appears predominantly cytoplasmic under normal cell culture conditions), is recuited to lysosomes upon nutrient depravation [21,22]. At the lysosome, FLCN/FNIP can interact with the RagGTPases, and *in vitro,* the complex possesses GAP activity towards RagC [22]. The Lst7/Lst4 complex functions in a similar manner at the yeast vacuole [5]. It is suggested that RagC GAP activity is important for amino acid dependent recruitment and activity of mTORC1 on lysosomes. This in turn regulates the activity of the lysosome associated transcription factors TFEB and TFE3, as loss of FLCN inhibits their phosphorylation, promotes their nuclear translocation and activity and drives lysosome biogenesis [20,21,23]. Thus, the lysosome is a key site of action of FLCN. However, whether

this pathway is sufficient to account for the broad and context dependent consequences of FLCN disruption is not clear.

Regulation of lysosome distribution by FLCN

During the course of our studies and consistent with work from the Rubinzstein lab, we noted that in HeLa cells, starvation not only promotes FLCN association with lysosomes, also results in a shift in their distribution in the cytoplasm [24,25]. In many cell types, including HeLa, lysosomes are typically localised throughout the cell with some enrichment proximal to the microtubule organising centre(MTOC)/Golgi which is typically in a perinuclear position. There is dynamic exchange between these populations [26]. Starvation causes a centripetal shift in that distribution with lysosomes concentrating in the perinuclear region [25]. We sought to understand whether this correlation of FLCN-lysosome association and propensity towards a starvation-induced perinuclear localisation were linked. Consistent with that proposition, depletion of FLCN or FNIP1/2 using RNAi suppressed starvation induced perinuclear clustering. Over-expression of FLCN and FNIP, whilst not strikingly impacting on steady state lysosome distribution, did promote the formation of dynamic tubules that extended from lysosomes, which have been linked to the activities of several small GTPases, their effectors and microtubule motor proteins.

We next considered the established pathways that control lysosome distribution and tubulation. To drive transport towards the plus end of microtubules that are typically located at the cell periphery, the lysosome associated small GTPase Arl8b recruits the adaptor protein SKIP (SifA and kinesin interacting protein) which in turn recruits kinesin-1 for plus end directed microtubule transport [27-29]. The recently described BORC complex initiates this process by recruiting Arl8b [30]. Kinesin-1 can also be recruited by Rab7 though its effector FYCO1 and a recent study has also suggested that kinesin-1 may also interact with phospholipids [31-33]. To promote transport towards the minus end of microtubules that are predominantly located in a perinuclear position at the microtubule organising centre, Rab7 can also recruit RILP (Rab interacting lysosomal protein) which in turn recruits cytoplasmic dynein [34,35] and indicates that lysosome-motor interactions may regulate bidirectional positioning upon microtubules. In addition to these lysosome intrinsic components, other reports have shown that the

lysosome extrinsic, predominantly Golgi localised, Rab34 and Rab36 GTPases can also impact upon lysosome distribution by promoting their perinuclear clustering. For Rab34, this also requires interaction with RILP [36-38]. Overall, it is likely that the summation of these opposing centrifugal and centripetal directed activities defines the dynamic distribution of the organelle.

We found that FLCN interacts directly with RILP using is C-terminal DENN domain (a protein fold that in other contexts has been linked to Rab GEF activity[8]), suggesting the possibility that FLCN may control lysosome distribution via this Rab effector. We also found that depletion of FLCN suppressed Rab34 induced perinuclear aggregation of lysosomes. Moreover, using an effector pull down assay, we noted that starvation increase the amount of Rab34 retained on GST-RILP resin, suggesting that activation of Rab34 may be metabolically regulated.

How does a predominantly Golgi localised GTPase control the distribution of lysosomes? One could envisage either a direct or indirect mechanism. In the indirect scenario, Rab34, via RILP would in some way signal to affect the activity of the lysosome associated transport components. Alternatively, Golgi localised Rab34/RILP may itself interact with lysosomes. A series of super resolution and ultrastructural imaging experiments strongly favoured the latter hypothesis – that Rab34 positive perinuclear membranes contact lysosomes. We showed that this association acts to limit lysosomal motility and so promotes their retention in this region of the cell.

We next sought to establish how FLCN could regulate these contacts, focusing on its DENN domain. Although many DENN domains act as Rab GEFs, we were unable to detect any Rab34 GEF activity from the FLCN-DENN *in vitro*. However, targeting of constitutively active Rab34 to mitochondria resulted in the DENN domain dependent re-localization of FLCN, suggesting that FLCN may interact with the active form of the GTPase. Went went on to show that the FLCN-DENN domain is capable of promoting the formation of the Rab34-RILP complex *in vitro*.

Thus, an attractive model presents itself - starvation-induced FLCN association with lysosomes drives dynamic, Rab34/RILP driven interactions between lysosomes and Golgi membranes that result in the limitation of their motility, promoting perinuclear retention and thus contributes to control of their cytoplasmic distribution (Figure 1). Whilst it is clear there is much work to do to fully understand the basis of these contacts, our studies did reveal the expression of RILP can promote

the association of Rab34 with Rab7. As RILP is a dimer [39,40], we speculate that this could form the basis of these contacts and that one role of the FLCN/FNIP complex is to promote their formation under conditions of nutrient stress.

Potential impacts of the dysregulation of lysosome dynamics

Together, these data suggest that FLCN may couple the lysosomal nutrient signaling network to the cellular machinery that controls the intracellular distribution of the organelle itself. This new mechanistic insight into the role of FLCN at the lysosome may have the potential to explain some of the diverse and context dependent phenotypes associated with its loss. The starvation induced perinuclear clustering of lysosomes has been suggested to be important in autophagic flux by promoting the fusion of lysosomes with autophagosomes [25]. Moreover, the localisation of lysosomes can affect mTORC1 activity, with higher activity associated with a more dispersed/peripheral localization [25]. Thus, the suppression of mTORC1 activity caused by loss of RagC GAP activity [22] may be counterbalanced by an opposing effect from a propensity towards peripheral distribution. Enhanced lysosomal biogenesis and/or exocytosis driven by the activation of TFEB/TFE3 would add a third variable [21,41]. The balance between these activities in various cell types could therefore give rise to the differing mTORC1 activity phenotypes found in various model systems studied.

Recently, the Grinstein lab has elegantly demonstrated that the position of lysosomes can directly control their luminal pH, with lysosomes at the cell periphery tending to be less acidic compared to the perinuclear population [42]. This may due to more limited access to the biosynthetic pathway, greater proton leakage and reduced vATPase (proton pump) activity. This in turn impacts on the degradative capacity of the Cathepsin L protease. RILP was recently reported to interact directly with the vATPase and regulate its activity, suggesting a potential mechanism that may couple positioning and acidity [43].

The distribution of lysosomes also affects their interaction with other organelles. A recent report suggested Rab34 may respond to extrinsic stimuli (LPS) to promote context-dependent changes in lysosome distribution to modulate lysosome fusion with phagosomes and control antigen cross presentation in dendritic cells [44]; it would be interesting to determine whether FLCN may also contribute to this pathway.

Similarly, elevation of intracellular calcium triggers lysosome exocytosis to participate in plasma membrane repair [45] and blocking lysosome transport to the cell periphery reduces cell spreading, migration and invasion [30,46].

Thus, a lack of capacity to control organelle dynamics in response to metabolic cues has the potential to impact on a wide range of cellular functions. A better understanding of these effects could help to unify the often seemingly disparate phenotypic and mechanistic data on FLCN.

Future Directions

As described above, a clear priority now is to understand more broadly the role of lysosome distribution/dynamics in normal cell function and in BHD syndrome. However, it is worth considering earlier work on the yeast homologue of FLCN, Lst7. Identified in a genetic screen as synthetically lethal with a temperature sensitive Sec13 mutant, Lst7 plays a key role in the transport of the Gap1p general amino acid transporter to the yeast cell membrane [47]. Given the central role of lysosome associated amino acid transporters in nutrient signalling, further work should explore whether the FLCN/FNIP complex also regulates trafficking of these proteins in mammalian cells. One attractive hypothesis is that lysosome-Golgi contacts described in our study may form part of a trafficking pathway [48]. Another recent study has described a key role for the lysosomal calcium channel TRPML1 in promoting the serum starvation dependent translocation of lysosomes to the perinuclear region via ALG-2 and cytoplasmic dynein, independently of Rab7 [49]. It seems possible that the TRPML1-ALG-2-dynein axis may initiate a net minus end bias in MT transport of lysosomes to the perinuclear region and this positioning is subsequently stabilised by Rab34. FLCN/FNIP induced lysosomal tubules also appear not dissimilar to those tubules that emerge from autolysosomes that participate in lysosomal reformation[31]. Future studies should explore whether the FLCN/FNIP complex can also impact upon these pathways. Moreover, it is also clear that changes in cytosolic pH can affect lysosome transport, with extracellular acidification resulting in a transient decrease in intracellular pH promoting lysosome dispersion, whereas alkalinisation, which occurs during starvation, promoting perinuclear aggregation [50]. It may be the case that the lysosomal association of a number of these proteins may be regulated in part by cytosolic pH or lysosomal

membrane potential. Finally, our study highlights how cells can make acute adaptations to their intracellular transport pathways in response to changes in metabolic state; it seems likely that other mechanisms remain to be discovered.

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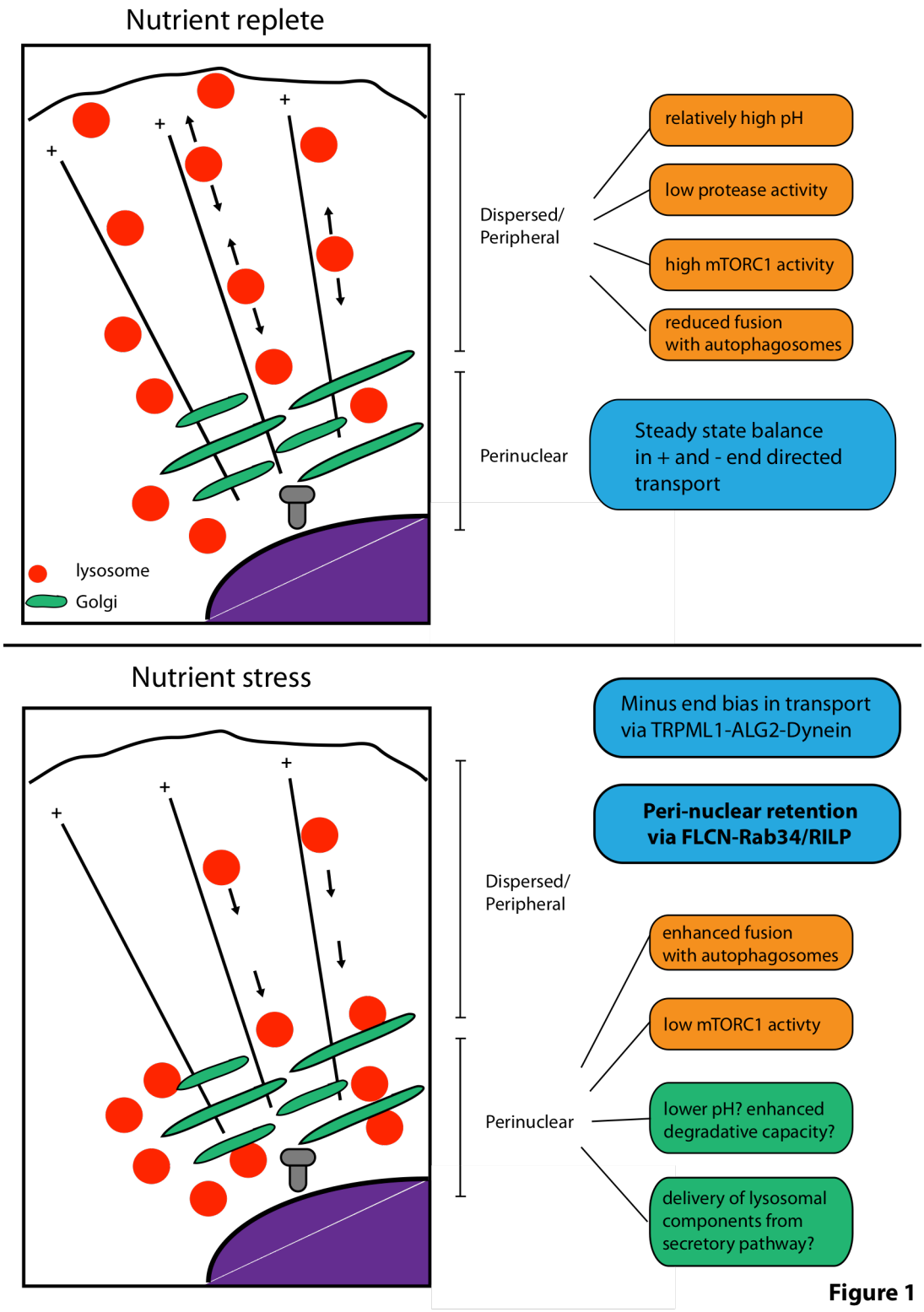

Figure 1

Legend

Diagram showing nutrient dependent changes in lysosome distribution, highlighting potential consequences for mTORC1 activity, lysosomal pH and degradative functions.