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Metabolic regulation through the endosomal system

Jerome Gilleron¹, Jantje M. Gerdes^{2,3} and Anja Zeigerer^{4,3,5}

¹ Université Côte d'Azur, Institut National de la Santé et de la Recherche Médicale (Inserm) UMR1065, Mediterranean Center of Molecular Medicine C3M, France.

² Institute for Diabetes and Regeneration, Helmholtz Center Munich, 85764 Neuherberg, Germany

³ German Center for Diabetes Research (DZD), 85764 Neuherberg, Germany

⁴ Institute for Diabetes and Cancer, Helmholtz Center Munich, 85764 Neuherberg, Germany and Joint Heidelberg-IDC Translational Diabetes Program, Inner Medicine 1, Heidelberg University Hospital, Heidelberg, Germany

⁵ Correspondence to: anja.zeigerer@helmholtz-muenchen.de

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Synopsis

This review explores how the endosomal system regulates glucose and lipid metabolism *in vivo* in mice and humans. It demonstrates the pivotal functions of endocytic trafficking in sensing extracellular metabolic cues and integrating this information to adapt to the alterations in metabolic homeostasis. Overall, this work highlights exciting new roles of the endosomal system on a higher physiological level and opens up a possible new direction for endosomal research.

Abstract

The endosomal system plays an essential role in cell homeostasis by controlling cellular signaling, nutrient sensing, cell polarity and cell migration. However, its place in the regulation of tissue, organ and whole body physiology is less well understood. Recent studies have revealed an important role for the endosomal system in regulating glucose and lipid homeostasis, with implications for metabolic disorders such as type-2 diabetes, hypercholesterolemia and non-alcoholic fatty liver disease. By taking insights from *in vitro* studies of endocytosis and exploring their effects on metabolism, we can begin to connect the fields of endosomal transport and metabolic homeostasis. In this review, we explore current understanding of how the endosomal system influences the systemic regulation of glucose and lipid metabolism in mice and humans. We highlight exciting new insights that help translate findings from single cells to a wider physiological level and open up new directions for endosomal research.

Introduction

The role of the endosomal system in maintaining cellular homeostasis has been studied for decades and has provided us with a deep appreciation for its complexity, specificity and functionality¹⁻⁴. This homeostasis is mediated by a highly interconnected network of compartments that regulate cellular signaling, nutrient sensing and transport, cell polarity and cell migration. The dynamic interaction between the endosomal

compartments enables the amount and spatial distribution of more than 5000 integral membrane proteins to be controlled^{5,6}. This function is accomplished by numerous endosomal multi-protein complexes that regulate the amount of proteins on the plasma membrane depending on the physiological condition by sending them to lysosomes for degradation or routing them back to the plasma membrane for recycling. Many elegant studies have unraveled the functions of the endosomal network within cellular systems. However, we have very limited knowledge on how these functions relate to the role of cells in tissues, organs and whole organism physiology.

Interestingly, recent findings have begun to support a role for the endosomal system in metabolic homeostasis. For instance, reduction of the endo-lysosomal compartments in the liver through knockdown of the small GTPase Rab5 was sufficient to induce a severe metabolic phenotype^{7,8}, normally only achieved through interference with metabolically relevant genes. This rapid and profound effect of Rab5 knockdown places the endosomal system into the regulatory network of glucose and lipid metabolism. Although these results might have been surprising, data in humans with metabolic diseases already show that mutations in endosomal genes are associated with metabolic pathologies, such as type-2 diabetes, hypercholesterolemia and non-alcoholic fatty liver disease (NAFLD)⁹⁻¹⁷. These recent findings highlight a wider function of the endosomal system at an organism level and provide us with a possibility to connect and translate our fundamental knowledge on endocytosis to metabolic (patho-) physiologies. In light of the increasing pandemics of type-2 diabetes and obesity, which will collectively affect 2 billion people worldwide by 2040 (WHO), this research could also reveal potential new targets for therapeutic interventions.

A key feature of type-2 diabetes is the dysregulation of metabolic homeostasis. This is characterized by an imbalance between nutrient intake, storage and consumption. Under physiological conditions, metabolically active organs, such as muscle, fat, liver, pancreas and brain, store nutrients upon food intake by turning on anabolic processes, such as glycogen and fatty acid synthesis and glycolysis, and by repressing catabolic

processes, such as gluconeogenesis (glucose production), glycogenolysis and fatty acid oxidation (**Figure 1**). When nutrient availabilities are low during fasting, these responses are inverted to ensure sufficient energy supplies for the body (**Figure 2**). The switch between fasting and feeding is mainly regulated by the hormones glucagon and insulin, where insulin is responsible for anabolic processes. This metabolic regulation is perturbed in type-2 diabetes, where constant food intake and endogenous energy production lead to a permanent increase in blood glucose levels (hyperglycemia) and insulin resistance. Thus, the maintenance of metabolic homeostasis requires proper sensing of insulin and glucagon signals and differential interpretation of those signals in different tissues. For instance, insulin induces glucose uptake in muscle and fat, but represses glucose production in liver (see below). In addition, the expression of nutrient transporters on the plasma membrane to mediate the uptake of glucose, low density lipoprotein-cholesterol (LDL-C), free fatty acids, etc. needs to be modulated in target tissues depending on nutrient availabilities. This implies a requirement for fine-tuned regulation of transporter recycling versus degradation. Plasma membrane plasticity is essential for internalization of receptors but also for secretion of insulin granules, for instance, in the pancreas. These different requirements for signal transduction, nutrient transport, receptor degradation and induced recycling are all hallmarks of the endosomal system.

This review will highlight how different levels of endosomal regulation can be integrated into our understanding of metabolic homeostasis and discuss components of the endocytic system that regulate systemic glucose and lipid metabolism, based mainly on *in vivo* studies in mice and humans. We will not address amino acid metabolism and lysosomal nutrient sensing via mTOR, as this has been discussed extensively elsewhere¹⁸⁻²⁰. Instead, we will focus on the parts of the endosomal system that contribute to metabolic control and potentially participate in the development of insulin resistance, hyperglycemia and steatosis (lipid accumulation within liver and muscle), leading to type-2 diabetes.

Regulation of glucose and lipid metabolism through the endosomal system

Glucose and lipid homeostasis are achieved by a balance between uptake of these nutrients, storage as glycogen or lipid droplets, and mobilization of those nutrient stores for energy production. The endosomal system participates in glucose and lipid uptake in the postprandial phase by regulating the expression of nutrient transporters and receptors on the cell surface. This can be achieved by enhanced recycling or reduced internalization. Upon surface appearance, nutrients can either bind to their receptors and be internalized, as exemplified by the LDL receptor (LDLR), or be actively transported into the cell, as in the case of fatty acids and glucose.

Regulation of glucose uptake and storage

Glucose uptake is induced upon food intake, when nutrients are enriched and blood glucose concentrations rise (**Figure 1**). This induces the secretion of insulin from the β -cells of the pancreas, which leads to the uptake of glucose into peripheral tissues, such as adipose tissue and muscle, causing blood glucose levels to drop. Internalized glucose is used for the build up of glycogen in muscle or is metabolized through glycolysis to be incorporated into fatty acids for storage in fat. The uptake of glucose is mediated by the insulin-dependent recruitment of the glucose transporter, GLUT4 from intracellular storage vesicles (GSVs)²¹.

Glucose transport through GLUT4

The regulation of GLUT4 trafficking is one of the best examples of how endosomal transport participates in metabolic control. Many detailed mechanistic studies describing the intracellular transport steps of GLUT4 have been performed in cell lines, and these have been discussed in many elegant reviews²¹⁻²⁵. In this review, we will focus instead on *in vivo* studies, where components of the endosomal system have been shown to affect

GLUT4 trafficking in tissues with immediate impact on systemic metabolism, and which are affected in metabolic disorders in humans.

As a transporter that cycles between intracellular compartments and the plasma membrane, GLUT4 traffics through all stages of the endosomal system, hence it is not surprising that many endosomal proteins have been shown to affect the behavior of GLUT4. Starting at the plasma membrane, dynamin2 was shown already in the late 90s to be required for GLUT4 internalization in primary rat adipocytes²⁶, which is consistent with its role in endocytic vesicle scission. Mutations in DNM2 have been linked to centronuclear myopathy (CNM), a diabetic late complication involving impaired actin-dependent trafficking in human muscle cells⁹. Interestingly, biopsies of patients with CNM reveal aberrant perinuclear accumulation of GLUT4, underscoring the importance of dynamin2 in internalization and actin remodeling even in humans⁹. In diabetes-induced nephropathy, induction of actin-dependent dynamin oligomerization has been shown to improve renal health in models of transient and chronic kidney diseases, which is relevant for diabetes-induced renal dysfunction²⁷. Whether this is mediated through the spatiotemporal reorganization of cell surface molecules upon dynamin activation or alterations in signaling properties in diverse models of transient kidney diseases remains to be elucidated.

Upon internalization, GLUT4 traffics through the early endosomes, where the requirement for early endosomal Rabs, such as Rab4 and Rab5, has been shown in 3T3-L1 adipocytes *in vitro*²⁸⁻³³. Here, Huang et al.³² raised the interesting idea that insulin inhibits Rab5 activity and the interaction of dynein with microtubules, and that these effects may inhibit the rate of GLUT4 internalization, resulting in enhanced surface expression of GLUT4. Whether this mechanism affects the presence of GLUT4 at the cell surface in adipose tissue and muscle in mice *in vivo* needs to be determined. Whole-body knockout mice for Rab4a and Rab4b display a reduction in circulating triglycerides and an increase in their total body fat mass, respectively, indicating a function of Rab4 in lipid metabolism (IMPC). The phenotype of Rab4b knockout mice could be in part due to the key role of

Rab4b in adipose tissue T cells, as was recently demonstrated³⁴. After passing through early endosomes, GLUT4 traffics through the endosomal recycling compartment, involving Rab11. Although Rab11 has been shown to be required for proper GLUT4 trafficking in adipocytes *in vitro*³⁵, its function in metabolic regulation *in vivo* remains unclear. Whole-body knockout mice indicate an essential role for Rab11a in development, whereas Rab11b knockout mice have no phenotype (IMPC). Only knockout mice of a Rab11 interactor, Rab11-FIP3, exhibit decreased body fat accumulations (IMPC). However, how this connects to GLUT4 trafficking and glucose homeostasis still needs to be elucidated.

An interesting feature of the recycling endosomes is to sequester cargo into a specialized recycling compartment, which is utilized in many tissues to specifically initiate the delivery of these cargoes to the plasma membrane in response to stimuli. This feature is used in GLUT4 trafficking for targeting of GLUT4 to the cell surface in adipocytes and muscle cells. Interestingly, in addition to GLUT4, the delivery of aquaporins to the basal membrane in the kidney³⁶ or the transport of bile acid transporters to the apical bile canaliculi in hepatocytes³⁷ is mediated via a similar storage compartment, highlighting a common concept of cargo sequestration and recruitment in physiology.

GLUT4 is retained in a specialized intracellular compartment and is targeted to the plasma membrane via insulin-regulated vesicular trafficking^{21,23}. Insulin induces an inactivation of the Rab GTPase activating proteins (GAPs) necessary for GLUT4 translocation, namely TBC1D4/AS160 and TBC1D1. This is achieved by an AKT-dependent phosphorylation of these Rab-GAPs, leading to a loss of their inhibitory role on the downstream Rabs necessary for GLUT4 trafficking to the cell surface. The Rabs for GLUT4 include Rab8a, Rab13 and Rab14 in muscle cells³⁸⁻⁴⁰ and Rab10 and Rab35 in adipocytes⁴¹⁻⁴³. While many elegant studies have unraveled the function of these Rabs and other interacting proteins in cell lines (for detailed review see²¹), only Rab10's function has been elucidated in mice. Adipose-specific knockout of Rab10 causes a 50% reduction in insulin-stimulated glucose uptake and GLUT4 translocation to the plasma membrane in fat, leading to a near complete failure of insulin to suppress hepatic glucose production

without significant inhibition of muscle glucose uptake⁴⁴. These data indicate that the amount of glucose uptake in adipocytes is a measure of whole-body glucose homeostasis that affects liver insulin sensitivity. Interestingly, Rab10 has been shown to interact with Sec16a, which is important for the biogenesis of GLUT4 transport vesicles at the TGN, suggesting a cooperative action of GLUT4 vesicle recycling and accelerated biogenesis to maintain the elevated cell-surface expression of GLUT4 under insulin stimulation⁴⁵. It will be interesting to see the role Rab8a and Rab13 play in muscle tissue *in vivo* and how interfering with their function affects GLUT4 trafficking and whole body glucose homeostasis.

The fusion of GLUT4 containing vesicles (GSVs) with the plasma membrane is an essential aspect in GLUT4 translocation upon insulin stimulation and has been extensively reviewed⁴⁶. This process has been shown to require Munc18c in 3T3-L1 adipocytes⁴⁷. Interestingly, heterozygous Munc18c knockout mice show a decrease in GLUT4 translocation in skeletal muscle and alterations of glucose-stimulated insulin secretion in pancreatic islets. This leads to severe glucose intolerance upon feeding a high fat diet, suggesting its importance not only for regulation of GLUT4 traffic but also other processes in β -cells⁴⁸.

Altogether, these data support an essential function of the specialized recycling compartment in regulating GLUT4 distribution and glucose transport that is essential in whole body glucose homeostasis. In fact, it has been shown that defective GLUT4 translocation is a strong feature of insulin resistance and type-2 diabetes in humans¹²⁻¹⁴. In addition, variants in the clathrin heavy chain CHC22 in humans are associated with altered GLUT4 trafficking and correlate with impaired GLUT4 translocation observed in type-2 diabetes¹⁵. These data underscore the important contribution of the endosomal system in proper GLUT4 trafficking, where many components have been studied in cell lines. Since GLUT4 traffics through many stages of the endosomal network throughout its cellular cycles, it is not surprising that many components affect GLUT4 behavior. However, it would be interesting to see whether these components are altered in diabetic conditions

and how trafficking of GLUT4 might change in diabetes. Trafficking studies in isolated primary adipocytes from diabetic mice might give answers in this direction.

Glucose transport through GLUT1 and GLUT2

Other glucose transporters, such as GLUT1 and GLUT2 are not insulin dependent. GLUT1 is expressed in all cell types and is responsible for steady-state uptake of glucose. Interestingly, depletion of the retromer complex, which is involved in the retrieval of cargoes back to the TGN^{5,6,49,50}, was shown to enhance degradation of GLUT1 and reduce cellular glucose uptake⁵¹⁻⁵⁴. The retromer complex is composed of a VPS complex (Vps35, Vps29 and Vps26), which engages cargoes, and a sorting nexin- Bin/amphiphysin/Rvs (SNX-BAR) complex (SNX1, SNX2, SNX3, SNX5, SNX6 and SNX27), which bends the membrane (for review see^{6,55}). The whole-body knockout mice of the core component of the retromer complex, Vps35, are embryonically lethal⁵⁶, but whole-body heterozygous depletion is not associated with a specific phenotype (IMPC). Consistent with these observations, knockout of the cargo adapter proteins SNX3 and SNX27 are homozygous lethal or sub-lethal (IMPC), suggesting that the retromer complex is essential for cellular homeostasis.

GLUT2 is expressed on β -cells and in the liver. It has not been shown to be sequestered into storage vesicles or to be recruited upon stimulation. In the liver, GLUT2 is a bi-directional transporter that internalizes and secretes glucose depending on its intracellular and extracellular concentration⁵⁷. In the postprandial state, glucose is taken up into the liver and used mainly for glycogen production (**Figure 1**). This glycogen can then be used for maintaining blood glucose levels under starvation. The reduction of blood glucose concentrations induces the release of glucagon from the α -cells of the pancreas, causing the breakdown of glycogen and induction of glucose production through gluconeogenesis in the liver, resulting in normalization of blood glucose concentrations (**Figure 2**).

In rodent β -cells, GLUT2 is the principal glucose transporter, while in human β -cells both GLUT1 and GLUT2 are involved in glucose transport^{58,59}. Interestingly, *GLUT2/SLC2A2* variants confer Type 2 diabetes risk, indicating that GLUT1 and GLUT2 function is not completely redundant⁵⁸. Importantly, extra- and intracellular glucose concentrations equilibrate quickly in pancreatic islets, suggesting that glucose transport is not the rate-limiting step in β -cell glucose metabolism. Instead, β -glucokinase (GCK/ hexokinase 4) activity is crucial to keep glucose inside the cell and to initiate glycolysis⁶⁰. Glucose-dependent mitochondrial ATP production in turn initiates insulin secretion by closing ATP-dependent K^+ -channels and subsequent opening of voltage-gated Ca^{2+} -channels⁶¹.

The trafficking of GLUT2 was found to be controlled by the Wiskott-Aldrich syndrome protein and SCAR Homologue (WASH) complex in mouse pancreatic β -cells. Indeed, pancreas-specific deletion of the WASH component WASHC1 causes intracellular accumulation of GLUT2 and decreased GLUT2 protein levels leading to impaired blood glucose clearance and reduced insulin secretion⁶². Because the WASH complex, composed of WASHC1, WASHC2, WASHC3, WASHC4 and WASHC5, is an important player in the retrieval of cargoes from the endosomes (for review see⁶), it is likely that WASH complex depletion enhances protein degradation upon reduced protein retrieval. Whether the retrieval of cargo through the WASH complex is sensitive to extracellular metabolic cues remains to be determined. However, it is important to realize that glucose uptake via GLUT2 in β -cells seems to be mainly observed in rodents, whereas humans internalize glucose also through GLUT1^{58,59}, making the direct translation of these trafficking studies to the human situation difficult.

An important part of glucose uptake is the adequate release of insulin from β -cells. This is mediated in a bi-phasic mode, where pre-docked and ready to fuse insulin secretory granules are secreted in the first phase of glucose-induced insulin secretion happening in seconds. The second phase insulin secretion requires re-internalization of the machinery necessary for insulin granule production and trafficking, where endocytosis

plays an important role. Here, rearrangements of the actin cytoskeleton are needed for proper insulin secretion. Components of the endosomal machinery, such as Cdc42 have been implicated in this process. Knockdown of Cdc42 in isolated mouse islets results in the selective loss of the second phase insulin release, potentially causing less insulin secretion, which could lead to an increase in blood glucose levels⁶³. In fact, islets from donors with type-2 diabetes have profound defects in glucose-stimulated Cdc42-PAK1 activation and insulin secretion, which might contribute to the failure of the β -cells to secrete insulin in diabetes⁶⁴. Here, it is suggested that glucose induces the translocation of Cdc42 to the plasma membrane, which activates the Cdc42-PAK1-RAC1 pathway, leading to cytoskeletal rearrangements and enhanced fusion of insulin granules with the plasma membrane⁶⁴. In addition, β -cell-specific inducible DMN2 knockout mice show a requirement for dynamin2 in glucose tolerance and proper glucose-induced second phase insulin secretion in mice⁶⁵. Interestingly, the decrease in insulin secretion is due to a disorganization and enhancement of the actin cytoskeletal network⁶⁵, which underscores a function for dynamin2 in plasma membrane actin remodeling that is not directly related to its role in vesicle scission.

Regulation of LDL-C uptake

The uptake of LDL-C by the liver is crucial for lipid homeostasis. In hepatocytes, internalized cholesterol esters in LDL are hydrolyzed to free cholesterol in late endosomes/lysosomes. Subsequently, through the Nieman-Pick Type-C proteins, cholesterol is further transported to other cellular compartments and either used as a component of intracellular membranes⁶⁶ or metabolized into bile acids and released into the bile canaliculi⁶⁷. Through this, the liver can actively reduce whole-body cholesterol levels via LDL-C endocytosis. A common feature of type-2 diabetes is hypercholesterolemia and fatty liver disease, which can develop through reduced uptake of LDL-C or enhanced secretion of very low density lipoprotein (VLDL) from the liver. Thus, by altering LDLR trafficking, endocytosis participates actively in LDL-C clearance. While it

was thought that the recycling of receptors, including the LDLR, is a relatively passive process following bulk flow⁶⁸, recent evidence has clearly illustrated that these trafficking processes are spatially and temporally regulated by a large number of multi-protein complexes^{5,6,49,50,69}.

Underlining the pivotal role of endocytosis on LDLR trafficking, we previously demonstrated that the depletion of Rab5 in mouse liver *in vivo* leads to a decrease in LDL-C uptake due to failure of LDLR internalization^{7,8}. In this study, we took advantage of a hepatocyte-specific delivery system, where siRNAs encapsulated into lipid nanoparticles are exclusively taken up by the liver⁷⁰, inducing a tissue-specific knockdown of Rab5 in adult mice. The defects in LDL-C uptake were sufficient to induce hypercholesterolemia and hyperlipidemia in the blood of these animals. Remarkably, depletion of Rab5 was sufficient to abolish the biogenesis of early endosomes causing a reduction of the entire degradative pathway⁷, making the dissection of the metabolic phenotypes and underlying molecular mechanisms challenging.

The role of the retriever-CCC-WASH complex in controlling lipid homeostasis

The retriever-CCC-WASH complex participates in cargo sorting⁶ downstream of Rab5 by recruiting F-actin onto endosomes via the WASH complex, as described above, recognizing cargoes via the CCC complex (COMMD, CCDC22 and CCDC93) and sorting them via the retriever complex (DSCR3, C16orf62 and Vps29). Interestingly, this large complex was also found to be implicated in lipid homeostasis. Indeed, patients with X-linked intellectual disability (XLID) involving a CCDC22 p.T17A or CCDC22 p.Y557C mutation were found to have an increase in total plasma cholesterol and LDL-C levels⁷¹. Moreover, liver-specific COMMD1 knockout mice show elevated plasma LDL-C and exhibit a mislocalization of LDLR associated with decreased LDL-C uptake in the liver⁷¹. COMMD1 is the founding member of a family of ten proteins expressing the Copper Metabolism MURR1 Domain (COMMD) at their carboxy terminus. All are able to engage the CCC complex to fulfill their discrete functions, including cell proliferation, copper homeostasis

and regulation of NF- κ B and sodium channels activities⁷²⁻⁷⁵. Strikingly, the increase in plasma cholesterol in liver-specific COMMD1, COMMD6, or COMMD9 knockout mice causes an exacerbation of atherosclerosis, highlighting a collective function of COMMDs and CCC components in modulating plasma lipid levels in humans¹⁰.

Considering the large number of nutrient transporters and receptors trafficking through the endosomal system, which all need to escape degradation, it seems likely that additional functions of the CCC-WASH-retriever complex and the retromer complex will be discovered. It will be interesting to see how cargo specificity in the retrieving pathway is achieved and how this is physiologically regulated. Recently, an elegant study has suggested that the adaptor protein PID1, which regulates whole body glucose homeostasis⁷⁶, is an insulin-dependent molecular switch that regulates the cellular distribution of another cholesterol transporter, LRP1 (low density lipoprotein particle related protein 1), and functions in the postprandial state by controlling SNX17 binding to LRP1⁷⁷. Interestingly, the CCC complex is also required for LRP1 trafficking to the plasma membrane, suggesting that this complex could mediate the insulin-dependent regulation of LRP1 trafficking via PID1^{10,71}. Whether this is regulated through a direct interaction with the CCC-WASH-retriever complex with PID1 still needs to be determined.

In addition to LDLR trafficking, endocytosis participates in the regulation of cholesterol flux within cells, which requires the function of Niemann-Pick type C (NPC) proteins. Indeed, mutations of Vps53 prevent the proper sorting of NPC2 to lysosomes, causing cholesterol accumulation⁷⁸. Vps53 is a common component of two complexes, the endosome-associated recycling protein (EARP) and the Golgi-associated retrograde protein (GARP), which are implicated in the tethering of cargo-containing carriers sorted from the endosomes to direct them either to the recycling compartments or the TGN, respectively (for review see⁷⁹). Consistent with this finding, mutation of the specific component of the GARP complex, Vps54, in human amyotrophic lateral sclerosis (ALS) patients and in wobbler mice was found to be associated with a dysregulation of energy

metabolism^{11,80,81}. In wobbler mice, these energy metabolism defects were linked to a disturbance of cholesterol homeostasis⁷⁸, suggesting that the GARP complex may be involved in the regulation of cholesterol flux. However, this needs to be confirmed, because EARP and GARP complexes share one quarter of their components, such that affecting one complex may alter the other.

Altogether, these results show that the retrieval of cargoes from endosomes has important implications for lipid and glucose metabolism. This could be a consequence of cargo recycling to the plasma membrane that requires this sorting step. Whether this retrieval is controlled by extracellular stimuli that initiate the recycling of nutrient receptors to the cell surface remains to be seen, but it would provide an interesting mechanism to explain how metabolic cues and conditions could influence cargo retrieval.

Metabolic signal processing through the endosomal system

Regulation of insulin and glucagon receptor trafficking

The regulation of the fasting/feeding transition is mediated by the action of insulin, glucagon and glucocorticoids. While the latter functions mainly through its nuclear receptor⁸², insulin and glucagon signaling is mediated through their plasma membrane receptors. Extensive studies have investigated the role of the endosomal system on insulin receptor (IR) signaling and trafficking in cell lines⁸³. Insulin receptor is internalized by clathrin-dependent pathways^{84,85} but also through caveolin-mediated uptake^{86,87}, suggesting that both processes exist and the receptor might utilize the different endocytic entry routes depending on the insulin receptor isoform, cell types and ligands. Nevertheless, the insulin receptor has been shown to localize to caveolae in adipocytes and myotubes^{86,88}, and this localization seems to be essential for proper insulin signaling, which was found to require caveolin1 in adipocytes and caveolin3 in muscle cells⁸⁸⁻⁹⁰. Indeed, the depletion of CAV1 or CAV3 in mice leads to insulin resistance in adipose tissue

and muscle, respectively^{91,92}. Importantly, the failure in insulin sensing by adipocytes results in a reduction in GLUT4 translocation (see above) and consequently reduced glucose storage into triglycerides, which could explain the lean phenotype and the resistance to diet-induced obesity in caveolin1 knockout mice⁹³.

Besides these studies in caveolin knockout mice, there are very few examples that investigate whether components of the endosomal system alter IR signaling and insulin sensitivity *in vivo*. The reason for this could be that the active internalized IR, which continues to signal on early endosomes⁹⁴, is more important for its mitogenic than its metabolic function⁹⁵. However, recent data have identified SORLA (sorting-related receptor with type A repeats, encoded by *SORL1*) as directing the IR back to the plasma membrane and enhancing IR signaling, thereby contributing to glucose intolerance and obesity⁹⁶. This highlights the importance of the balance between IR recycling and degradation for metabolic control.

The glucagon receptor is a prototypical G protein-coupled receptor, for which prolonged agonist stimulation attenuates signaling (homologous desensitization). However, internalization of the desensitized receptors and their sequestration into intracellular vesicles is a primary mechanism of signal attenuation and is essential for receptor resensitization (for review see⁹⁷). Internalization of the glucagon receptor is mediated by clathrin-dependent endocytosis in hepatocytes⁹⁸, as well as through caveolin⁹⁹. This dual mode of internalization may differ depending on the cell types and may have important consequences for signaling outcomes. However, it remains unclear whether endocytosis participates in glucagon signaling independently of its role in receptor distribution.

Signal interpretation through the endosomal system

While signaling receptor trafficking is important for signal transduction and downregulation, specific components of the endosomal system could play important roles in signal interpretation by interacting with downstream signaling receptor targets. Indeed,

the surface of endosomes functions as a platform for signaling domains¹⁰⁰ that control the spatiotemporal distribution of signaling molecules within the cell¹⁰¹. Interestingly, the Rab5 effector APPL (Adaptor protein containing PH domain, PTB domain and Leucine zipper motif) has been shown to interact with AKT2 on endosomes^{100,102}, suggesting a potential metabolic function. In fact, APPL1 was reported to interact with adiponectin, an adipocyte hormone that is important for glucose sensitivity and fatty acid oxidation¹⁰³. APPL1 has been shown to be necessary for adiponectin functions, such as lipid oxidation, glucose uptake and GLUT4 translocation in L6-myotubes¹⁰⁴. There, adiponectin stimulates the interaction between APPL1 and Rab5, leading to increased GLUT4 translocation. It would be interesting to see whether insulin influences this interaction in muscle.

Besides its function in mediating glucose uptake in fat and muscle, insulin also acts on the liver during feeding by reducing the expression of gluconeogenic genes, such as *Glucose-6-phosphatase (G6Pase)*, which is rate limiting for glucose output¹⁰⁵. This is achieved by AKT-mediated phosphorylation of Forkhead box-O1 (FOXO1), a main transcription factor for gluconeogenesis, resulting in FOXO1 inactivation¹⁰⁶. Since APPL1 has been shown to interact with the metabolically active isoform AKT2^{100,102}, it is not surprising that liver-specific overexpression of APPL1 by adenovirus results in increased hepatic insulin sensitivity and enhanced insulin-induced suppression of the gluconeogenic program¹⁰⁷, while its knockdown has the opposite effect. The improvement of insulin sensitivity is achieved by binding of APPL1 to AKT2, thereby preventing the interaction of AKT2 with its inhibitor Tribble3 (TRB3)¹⁰⁸, thus promoting AKT translocation to the plasma membrane and inducing enhanced AKT signaling. Interestingly, conditional deletion of APPL2 in skeletal muscle exhibits the opposite phenotype. Here, insulin-induced plasma membrane recruitment of GLUT4 and glucose uptake are impaired by APPL2 overexpression but are enhanced upon knockdown, leading to improved glucose tolerance¹⁰⁹. This is achieved by a direct interaction of APPL2 with the Rab-GTPase activating protein TBC1D1, which is necessary for GLUT4 translocation. Why APPL1 and APPL2 have these opposite effects and interaction partners, and how they are

physiologically regulated upon glucose challenge, remains to be elucidated. The pathophysiological significance of APPL1/2 for glucose homeostasis, however, is supported by observations in diabetic patients and patients with NAFLD, where loss-of-function mutations in APPL1 and genetic variation in APPL1/APPL2 loci are linked to familial forms of diabetes¹⁶ and hepatic steatosis¹⁷, respectively.

As APPL1 is a well-established Rab5 effector, one would assume that interfering with Rab5 would mimic the APPL1 phenotype in relation to insulin sensitivity and glucose production. Surprisingly, depletion of Rab5 in the liver *in vivo* had no effect on insulin signaling and insulin-induced AKT activation⁸. Nevertheless, we still observed a strong reduction in gluconeogenic genes causing an almost complete block of glucose output, thus inducing hypoglycemia. Usually, reduced blood glucose levels induce glucagon signaling, causing upregulation of gluconeogenesis through cyclic-AMP-mediated activation of protein kinase A (PKA). This results in phosphorylation and activation of the transcription factor cAMP responsive binding protein (CREB) and the expression of FOXO1, which function together to drive the gluconeogenic program^{105,110,111}. Despite activated PKA and enhanced cAMP production under Rab5 knockdown, the expression of FOXO1 and the CREB downstream target PPAR γ coactivator protein 1 α (PGC1 α) is strongly diminished, abolishing *G6Pase* gene expression⁸. However, how Rab5 affects CREB and FOXO1 function still needs to be determined. One possibility is that the endosomal membranes could serve as platforms for factors such as FOXO1 to interact with their signaling kinases, which regulate their activity. Upon loss of the endosomal membranes due to Rab5 knockdown⁷, those platforms are not available anymore, which actually leads to the observed redistribution of FOXO1 and CREB in the liver⁸. Importantly, *G6Pase* is highly upregulated in type-2 diabetic livers, which contributes to enhanced glucose production and hyperglycemia. Therefore it is intriguing to note that depletion of *Rab5* in diabetic *db/db* mice can rescue their elevated blood glucose levels by downregulating *G6Pase* expression⁸, highlighting a potential therapeutic application for metabolic diseases.

Further support for a function of early endosomes in metabolic signaling comes from studies interfering with the class III PI3 kinase, Vps34. Although Vps34 is not directly downstream of insulin signaling, knockouts of Vps34 and Vps15 in mice show enhanced insulin sensitivity and glucose tolerance, with reduced hepatic glucose production^{112,113}. The effect on glucose production was found to be due to a strong reduction of gluconeogenic genes in hepatocytes, caused by an alteration in insulin-induced AKT activation¹¹³. However, none of these approaches seem to reduce the number of endosomes, suggesting an alternative mechanism compared to Rab5 knockdown. Altogether, these data highlight unexpected functions of endocytic components on metabolic gene regulation, where the underlying mechanisms still need to be further explored.

Glucose-stimulated insulin secretion has been shown to depend on EphrinA (EFNA)/ EphrinA-receptor (EPHA) signaling¹¹⁴ and single-cell transcriptomics of human pancreatic islets revealed that the EPH-receptor and EFN-ligand family was significantly enriched¹¹⁵. In islets of a β -cell specific, inducible intraflagellar Transport 88 (*Ift88*)-knockout mouse model, EphA3 is hyperphosphorylated, blocking glucose-stimulated insulin secretion, resulting in reduced glucose tolerance¹¹⁶. In these cells, pEphA is not efficiently internalized and trafficked to the perinuclear region where the main protein tyrosine phosphatase is located that suppresses spontaneous, ligand-independent activation. This represents one example for metabolic defects related to impaired endosomal signal processing.

There are many more metabolic signaling receptors that are important for glucose and lipid homeostasis, such as the GIP receptor (GIPR), GLP1 receptor, leptin receptor, FGF21 co-receptors FGFR1 and β -Klotho, where we have yet to determine how they are trafficked through the endosomal system and whether the transport is important for receptor function. These receptors are expressed in many different tissues, such as adipocytes, which could be used to study their trafficking and signaling. In fact, activation

of GIPR by ligand binding in 3T3-L1 adipocytes has been shown to induce a slow recycling of GIPR without changing internalization, resulting in receptor desensitization¹¹⁷. Genome-wide association studies (GWAS) have shown that mutations of this receptor are associated with obesity, cardiovascular disease, and an increased risk for bone fractures in humans¹¹⁸⁻¹²⁰. These mutations cause enhanced receptor desensitization and downregulation¹¹⁷, underscoring how subtle changes in trafficking of GIPR impact human physiology. It will be interesting to see how these mutations affect the behavior of GIPR *in vivo* in mice and whether the induced metabolic alterations can explain the human correlations with obesity in these GWAS study.

The role of endosomal degradation in metabolic control

Degradation is an essential process in the regulation of energy homeostasis. This includes controlling the cellular amount of nutrient receptors or transporters, which are necessary for cargo entry. The degradation of activated signaling receptors is pivotal for signal downregulation to avoid prolonged signaling. In addition, the release of energy stored as macromolecules may require degradation processes through the lysosome.

Degradation of nutrient transporters/receptors

All cargo that has not been sorted in early endosomes for recycling through multiple recycling and retrieval complexes⁶ will be sent to lysosomes for degradation. Therefore, these retrieval complexes play essential roles in regulating the expression of nutrient transporters and receptors at the cell surface. We have already reviewed some of those in the section on nutrient uptake, where retromer was important for GLUT1 recycling^{53,54}, WASH complex for GLUT2 and LDLR^{62,71} and the CCC complex for LDLR and LRP1¹⁰. With so many nutrient transporters and receptors trafficking through the endosomal pathway, it will be interesting to see how their recycling and degradation are regulated, and whether the fate of these cargoes changes in metabolic diseases. One

could imagine that enhanced degradation of particular nutrient receptors, possibly through malfunction of the retrieval proteins, could participate in the metabolic imbalance observed in diabetes and obesity.

Degradation of signaling receptors

As discussed above, the signaling cascades that emerge following receptor-ligand binding regulate several metabolic functions. Importantly, these signals need to be transient to induce a proper cellular response and avoid continuous activation of cells. The signaling peaks are mechanistically achieved by desensitization of the signaling receptors mainly via their lysosomal degradation. Therefore, perturbing signaling receptor degradation may have an important metabolic impact. Consistent with this possibility, conditional knockout of EPN1 and EPN2 in lymphatic endothelial cells (LECs) prevent VEGF-C-induced vascular endothelial growth factor receptor 3 (VEGFR3) from endocytosis and degradation¹²¹. VEGFR3 is essential for lymphatic vessel growth and lymphangiogenesis, and was found to drop during diabetes¹²². Interestingly, the loss of lymphatic-specific epsins alleviates insufficient lymphangiogenesis in diabetic mice, indicating a novel approach to treating diabetic complications¹²².

Signaling receptors (mainly receptor tyrosine kinases) subject to degradation are marked by ubiquitination on lysine-63 and are recognized by the evolutionarily conserved endosomal sorting complexes required for transport (ESCRT) machinery, which drives membrane deformation and vesicle scission to generate cargo-enriched intraluminal vesicles (ILVs)^{123,124}. In theory, the ESCRT machinery should play an essential role in the degradation of metabolically active signaling receptors. Not many studies have elucidated their function in metabolic homeostasis, however, probably also because some components of this machinery are essential for embryonic development, leading to embryonic lethality in whole-body knockout mice (e.g. TSG101, CHMP3, CHMP6, CHMP7) (IMPC). However, one study has highlighted how activation of the ESCRT machinery seems to protect against NAFLD and non-alcoholic-steatohepatitis (NASH) development in mice

and monkeys, by targeting toll like receptor 4 (TLR4) for degradation¹²⁵. This suggests that interfering with ESCRT complexes in mice *in vivo* will reveal novel roles for the ESCRT machinery in glucose and lipid metabolism.

Degradation of macromolecules

To keep whole-body nutrient supplies constant during periods of fasting and feeding, energy stores in the form of fat and glycogen are built up in postprandial periods and mobilized under starvation. Although many endocytic processes are connected to nutrient uptake and storage (see above), the endocytic machinery is also useful for degrading macromolecular components. This includes processes related to lipid droplet and glycogen degradation. In relation to the endocytic system, Rab7 and Vps34, components that are shared between the endosomal and autophagic machinery, have been shown to be required for lipid droplet degradation via autophagy under nutrient starvation^{126,127}. Interestingly, knockdown of Vps34 in mouse liver causes hepatomegaly and liver steatosis, underscoring its physiological relevance¹²⁷. However, the role of Rab7 in lipophagy has only been investigated *in vitro*, and further studies *in vivo* are still required. Interestingly, caveolin1 has also been implicated in liver steatosis and lipid transport, underscoring the diverse function of caveolae in metabolic control¹²⁸.

Glycogen is another storage macromolecule that is pivotal to maintain blood glucose concentrations (see above). Strikingly, we previously found that depletion of Rab5 in mouse liver leads to a dramatic accumulation of intrahepatocellular glycogen contents^{7,8}. How the depletion of Rab5 could perturb glycogen breakdown is puzzling. One explanation is that the strong reduction in *G6Pase* expression, which is not only the rate-limiting gene in gluconeogenesis but also in glycogenolysis, could cause accumulation of glycogen. Alternatively, the endo-lysosomal system, which is abolished in the Rab5 knockdown, could be involved in glycogenolysis. Supporting this possibility, Pompe disease, a lysosomal storage disorder also known as glycogen storage disease type II, is caused by a mutation in the gene encoding the acid α -glucosidase (GAA), which localizes

to the lysosome to hydrolyzes glycogen to glucose¹²⁹. Cytosolic glycogen seems to be targeted to lysosomes in the process of autophagy to achieve its breakdown¹³⁰.

Altogether, lysosomal degradation is essential in metabolic homeostasis, which has already been well recognized. The components of the endosomal system that initiate the sorting of cargoes for degradation have not been studied intensively in metabolic control. These components are decision drivers that could alter metabolic outcomes by changing the fate of nutrient transporters and metabolic signaling receptors towards degradation or recycling. It would be interesting to see whether metabolic cues influence their expression. In fact, promotor analysis of over 2000 new knockout mouse strains revealed an unknown link between the ESCRT-III protein CHMP3 and metabolism. CHMP3 was amongst those candidates, and its promoter contains common regulatory elements functioning as transcription factor binding sites, which are co-regulated upon metabolic alterations¹³¹. This suggests a differential expression of at least CHMP3 in metabolic diseases. Whether this has functional consequences needs to be elucidated.

Conclusions and Outlook

In the present review, we have highlighted how endosomal trafficking integrates into metabolic homeostasis and focused on components of the endocytic system with existing mechanistic implications. Besides those, there are still a large number of endocytic factors that influence metabolism but for which we lack an understanding of how and why. This is especially true in invertebrate model organisms, where several genome-wide screens have been performed to identify genes implicated in either glucose or lipid metabolism. Strikingly, more than 30 endocytic components located all along the different endocytic pathways were found to impact glucose or lipid metabolism in *Caenorhabditis elegans*, *Drosophila melanogaster* or *Danio rerio*¹³²⁻¹⁴⁴ (see **Table 1**). Unfortunately, since these screens cannot reveal the mechanisms leading to changes in fat mass, glucose storage or catabolism, the metabolic functions of the identified genes

remain unclear. Similarly, numerous other components have been found to play a role in mammalian metabolism, but the mechanisms of action are still not well defined¹⁴⁵⁻¹⁵⁷ (see **Table 1**). Thus, despite the large number of endosomal proteins that are now known to participate in metabolic regulation, there are still many for which a metabolic function is implied but not really mechanistically demonstrated. Why is that and what can we do better?

Despite the recent advances in technology to study both endocytosis and metabolism in great detail, there is still little information on how these two modules are connected. These gaps in knowledge can be largely explained by two main limitations in current research that should be addressed. Firstly, endosomal trafficking and metabolism are mainly studied independently of each other, largely due to the complexity of both processes. Therefore, basic scientists and clinicians of even closely related fields often use different terminology and concepts, leading to an impression of speaking different “languages”. This makes the understanding and appreciation of each other’s work challenging. Secondly, endosomal transport processes are mainly studied in cells (*in vitro* systems). Basic knowledge obtained through these *in vitro* studies is rarely followed up by studies in mouse models and in humans (clinical samples), which hampers the translation of fundamental knowledge on endosomal transport into (patho-) physiological information and also potential clinical relevance. This is largely explained by the limited number of model systems available to study the endosomal system at an organismal level. Furthermore, a lot of sophisticated technologies are mainly applied to *in vitro* systems and not to *in vivo* systems, because of their restrictions, high costs or lack of knowledge regarding how to use them in more complex model systems (e.g. organoids and animal models). While the connection between endocytosis and gluco-lipid metabolism is becoming more evident, fruitful collaborations with other scientists equipped with animal facilities and established primary cell culture systems will enable a more *in vivo* oriented characterization of endosomal transport in metabolic control. In addition, shared conferences and research consortia could be initiated to bring together scientists from

both fields for discussions, exchange and inspiration. Apart from the collaborations that could arise from such initiatives, this would also help to establish a common language and understanding in the field.

There are many open questions that could be addressed following such a strategy. For instance, what is the function of the endosomal system in different metabolically active tissues? We have seen already that adipose and liver tissue fulfill very different functions. Further work should therefore extend and deepen these initial insights. Likewise, what is the function of the endosomal system in cells with minimal direct contribution to whole body energy metabolism? We recently demonstrated that depleting Rab4b in T cells was sufficient to alter adipose tissue function leading to liver steatosis and insulin resistance³⁴. Is the recycling of cargo through the retriever pathway, as shown for LDLR in the liver, similar in fat? The interesting data on the role of the WASH complex on GLUT2 trafficking opens up the possibility of a potential function of the retriever-CCC-WASH complex on GLUT4 *in vivo*, as has been suggested from adipocyte cell lines^{158,159}. Also, is the control of signaling through the endosomal system comparable between muscle and liver? For instance AKT2 activation induces very different responses in the muscle, where it induces glucose uptake, than in the liver, where it represses gluconeogenesis. The conflicting data on APPL1 and APPL2 in these tissues could be examples of tissue-specific regulation.

Interestingly, we also presented evidence that components of the endosomal system are altered upon different metabolic challenges and in metabolic diseases, such as type-2 diabetes and NAFLD. Further studies are necessary to elucidate the mechanisms underlying these observations. This would require culturing cells in more physiological conditions (between 5 mM and 11 mM glucose, which corresponds to 90 and 200 mg/dl blood glucose concentration, respectively) rather than exposing them to extremely high glucose levels of usually 25 mM, which translates into 450 mg/dl blood glucose values, usually only observed in severely diabetic and obese mice. Metabolically active cells will respond, when primed. For instance, studies in yeast have already shown that high

glucose stimulations induce the assembly of adapters and clathrin on the TGN and endosomes¹⁶⁰. In addition, expression analysis and functional assays can be performed in human tissues and mouse models of metabolic disease, respectively, to elucidate whether endosomal components and endocytosis functions properly in a diabetic or obese condition. There are many more endosomal components waiting to be studied, where exciting new functions of these components and endocytosis *per se* in metabolic control can be explored and unraveled. There are exciting times ahead for this emerging field.

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Figure Legends:

Figure 1: Involvement of endocytic components in systemic metabolism in the post-prandial (feeding) period.

After a meal, circulating blood glucose levels rise, leading to a massive entry of glucose into pancreatic β -cells via the glucose transporter GLUT2, which causes the release of insulin into the blood stream. The cell surface amounts of GLUT2 are maintained constant via recycling of GLUT2. Adipocytes, the main cell type of adipose tissue, sense the increase in circulating insulin levels resulting in an induction of p-AKT dependent signaling cascades that favor the fusion of GLUT4 storage vesicles with the plasma membrane, increasing the surface expression of GLUT4. When GLUT4 is translocated at the cell surface, glucose will enter into adipocytes and be stored as triglycerides within the lipid droplets.

Concomitantly, insulin acts on the main liver cells, hepatocytes, by inducing a cascade of signaling events downstream of the insulin receptor. These signals will restructure the genomic program of the hepatocytes towards anabolic processes, either storing glucose that enters the cells in a concentration-dependent manner via GLUT2 into glycogen, or utilizing the glucose for glycolysis. In addition to controlling glucose levels, hepatocytes also participate in the regulation of cholesterol levels. To achieve this function, circulating low-density lipoprotein cholesterol (LDL-C) is taken up by the hepatocytes and sent to lysosomes, where the digested cholesterol will be extracted via the Niemann-Pick proteins into the cytosol. Cytosolic cholesterol can then be used either for incorporation into membranes or for bile acid production. Examples of endocytic components that play a role in these metabolic processes are labeled in red. EE = early endosomes, ERC = endosomal recycling compartment, GSVs = GLUT4 storage vesicles, ISGs = insulin secretory vesicles, LYS = lysosome, TG = triglycerides, IR = insulin receptor, LDLR = LDL receptor, NPC= Niemann-Pick protein.

Figure 2: Involvement of endocytic components in systemic metabolism during the fasting period.

During fasting, blood glucose levels drop, leading to a reduction in insulin secretion by pancreatic β -cells. Instead glucagon is secreted from pancreatic α -cells, which mainly acts on hepatocytes and induces a signaling cascade that shifts the genomic program towards catabolism, producing glucose either by the breakdown of glycogen or *de novo* synthesis from pyruvate through gluconeogenesis. Hepatocytes will also produce energy by breaking down their triglyceride stores into non-esterified fatty acids (NEFA) and burning them via β -oxidation. Concomitantly, in the adipocytes, the drop in insulin will stop GLUT4 translocation, which will be removed from the plasma membrane through endocytosis and stored in GLUT4 storage vesicles, leading to the arrest of glucose uptake by the adipocyte. This is also accompanied by an activation of triglyceride lipolysis releasing glycerol and NEFA into the blood. Glycerol will be used by hepatocytes to generate

pyruvate essential for gluconeogenesis, and NEFA will be burned via β -oxidation. Examples of endocytic components that play a role in these metabolic processes are labeled in red. EE = early endosomes, ERC = endosomal recycling compartment, GSVs = GLUT4 storage vesicles, ISGs = insulin secretory vesicles, LYS = lysosome, TG = tryglycerides, GR = glucagon receptor, IR = insulin receptor, NEFA = non-esterified fatty acids.

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Adipose tissue adipocyte

Liver hepatocyte

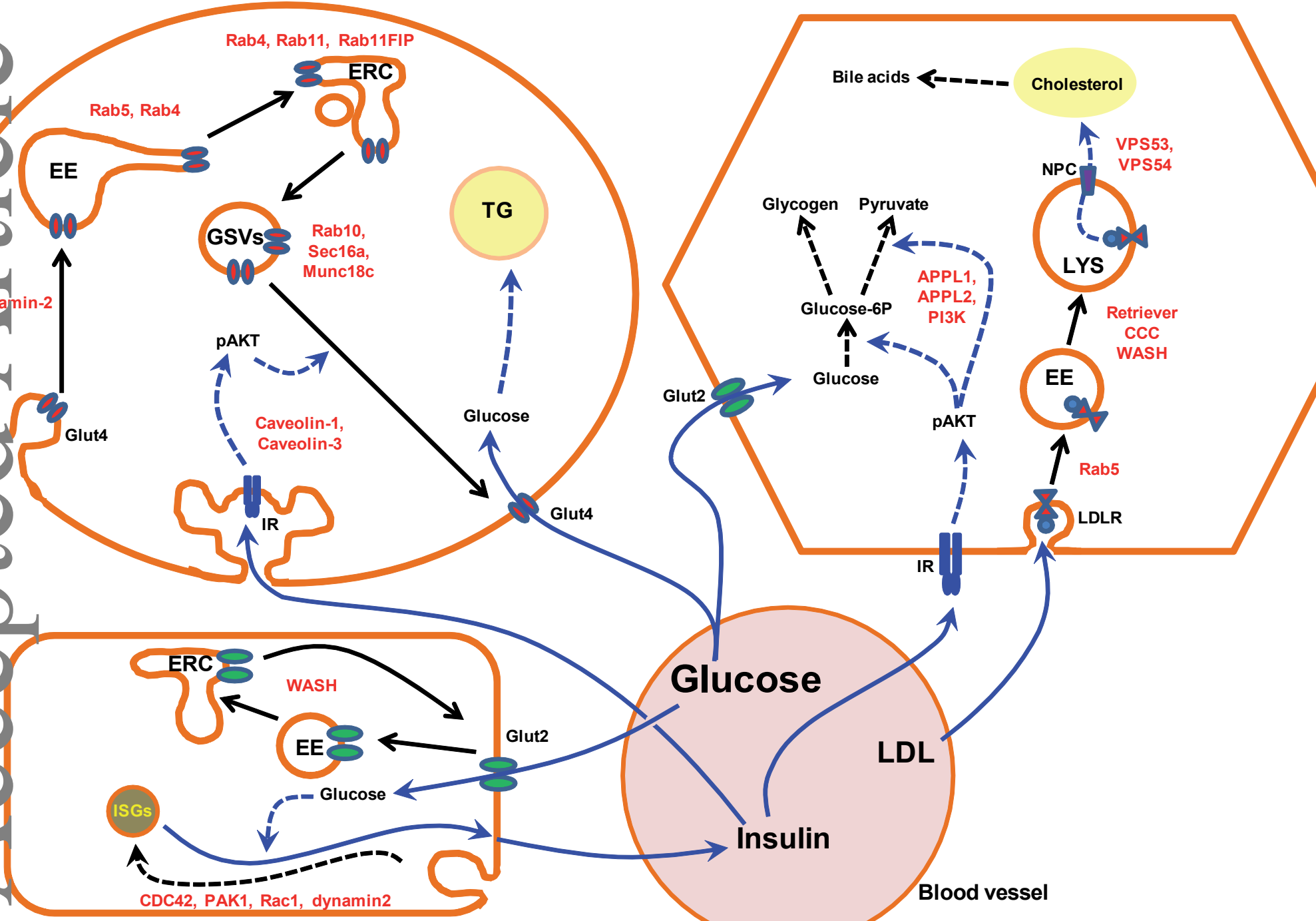


Figure 1

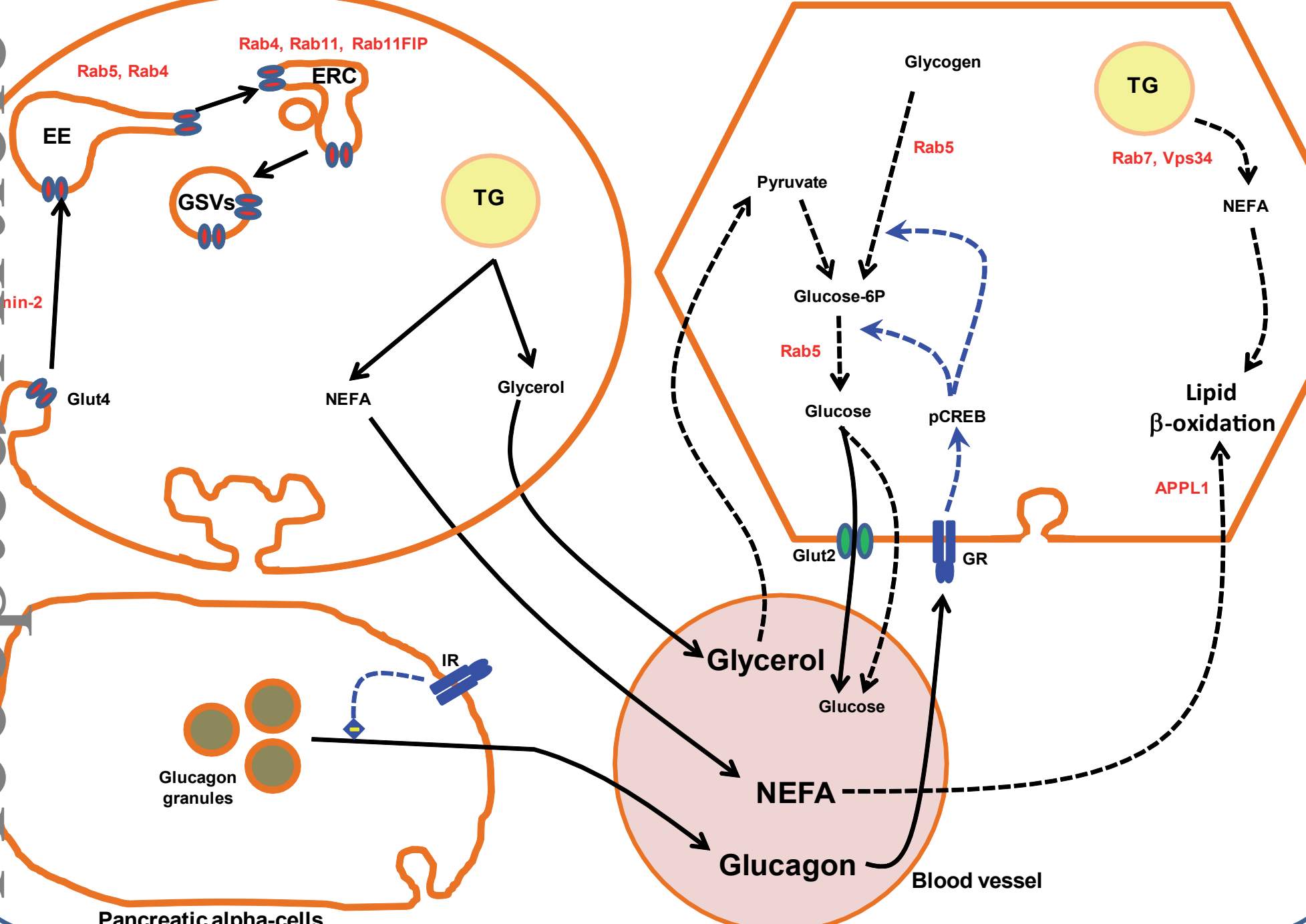
Adipose tissue adipocyte

Liver hepatocyte

Pancreatic alpha-cells

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Figure 2



Gene (complex)	Organism	Regulation	Metabolic/endocytic effect	Reference
Clathrin	C. Elegans	RNAi	Increase glucose metabolism	Lee et al., Dev Cell 2015
	Human	functional study & tissue specific o/e	Clathrin Heavy Chain Isoform CHC22 regulate GLUT4 compartment	Vassilopoulos et al., Science 2009
AP-2	C. Elegans	RNAi	Reduction of whole body fat content	Webster et al. Cell Reports, 2017
	C. Elegans	RNAi	Increase glucose metabolism	Lee et al., Dev Cell 2015
Dab2	Drosophila M.	RNAi	Reduction of whole body fat content	Pospisilik et al., Cell 2010
	Mice	KO	Defect in adipogenesis. Reduction of fat mass.	Tao et al., Sci Rep 2016
Epsin	C. Elegans	RNAi	Reduction of whole body fat content. Abnormal lipid metabolism	Ashrafi et al., Nature 2003
	Mice	LEC-iDKO	Epsin deficiency promotes lymphangiogenesis through regulation of VEGFR3 degradation in diabetes.	Wu et al., JCI 2018
Dynamitin	primary rat adipocytes	o/e of wt and GTPase def. dynamin 2	Dynamitin-2 is necessary for GLUT4 internalization	Al-Hasani et al., JBC 1998
	Human muscle cells	o/e of mutant Dynamitin 2	Dynamitin-2 mutations disrupted the formation of new actin filaments as well as the stimulus-induced translocation of GLUT4 to the plasma membrane.	González-Jamett et al., Sci Rep 2017
	Mice	small molecule,	Pharmacological targeting of actin-dependent dynamitin oligomerization ameliorates chronic	Schiffer et al.,

		dynamins 2 activator	kidney disease in diverse animal models.	Nat Med 2015
	Mice	dynamins 2 deletion in β cells	Dynamins-2 important for second phase insulin secretion.	Fan et al., JCI 2014
HSC70	Drosophila M.	RNAi	Reduction of whole body fat content	Pospisilik et al., Cell 2010
	STZ-induced diabetic rats	expression	Abundance of Hsc70 increased by insulin. Downregulation of Hsc70 in diabetic myocardium was secondary to insulin deficiency.	Chen et al., J Endocrinol 2006
Caveolin	C. Elegans	Null-mutant	Reduction of whole body fat content	Han et al., Protein Cell 2013
	Mice	Caveolin 1 KO	Caveolin-1-deficient Mice Are Lean, Resistant to Diet-induced Obesity, and Show Hypertriglyceridemia with Adipocyte Abnormalities. Caveolin-1-deficient mice show insulin resistance and defective insulin receptor protein expression in adipose tissue.	Razani et al. JBC 2002; Cohen et al., Am J Physiol Cell Physiol. 2003
	Mouse liver		Caveolin-1 Function in glucose and lipid metabolism in the liver.	Fernandez-Rojas MA & Ramm GA Trends Mol Med. 2016
	mouse adipocytes	localization	IR is highly enriched in caveolae structures by EM	Gustavsson et al., FASEB J 1999
	mouse adipocytes	RNAi by lentivirus	Caveolin-1 Loss of Function Accelerates Glucose Transporter 4 and Insulin Receptor Degradation in 3T3-L1 Adipocytes.	Gonzalez-Munoz et al., Endocrinology

				2009
Rho A	Drosophila M.	RNAi	Increase of whole body fat content	Baumbach et al., Cell Metab 2014
	C. Elegans	RNAi	Increase of whole body fat content	Webster et al., Cell Rep 2017
	mice	activation	Lipid-induced muscle insulin resistance through activation of the RhoA/Rho kinase signaling pathway.	Tao et al., JBC 2015
	mice	inhibitor	Rho-Kinase Inhibition Ameliorates Metabolic Disorders through Activation of AMPK Pathway.	Noda et al., Plos One 2014
	rats	activation through exercise	Short-term exercise increased insulin sensitivity and glucose tolerance through increased Rock activity and pIRS1.	Muñoz et al., J Cell Physiol. 2018
CDC42	Drosophila M.	RNAi	Hyperglycaemia	Ugrankar et al., Nat Commun 2015
	human islets	activation	Restoration of Glucose-Stimulated Cdc42-Pak1 Activation and Insulin Secretion by a Selective Epac Activator in Type 2 Diabetic Human Islets.	Veluthakal et al., Diabetes 2018
	human islets; mouse islets; mouse pancreatic cell lines	review	Cdc42: A Novel Regulator of Insulin Secretion and Diabetes-Associated Diseases.	Huang et al., Int. J. Mol. Sci. 2019
	Wistar rats, STZ & HFD diet	expression analysis	Increased cardiac expression of Cdc42 and Pak1 in diabetic hearts and in HG-treated cardiomyocytes.	Raut et al., Cardioasc Ther 2015
	mouse islets	RNAi	Glucose-stimulated Cdc42 Signaling Is Essential for the Second Phase of Insulin Secretion.	Wang et al., JBC 2007

Rab5	C. Elegans	RNAi	Reduction of whole body fat content	Mukhopadhyaya et al., EMBO Rep 2007 ; Webster et al., Cell Rep 2017 Mukhopadhyaya et al., EMBO Rep 2007
	C. Elegans	RNAi	Abnormal fat localization	Lee et al., Dev Cell 2015
	C. Elegans	RNAi	Increase glucose metabolism	Ugrankar et al., Nat Commun 2015
	Drosophila M.	RNAi	Hyperglycaemia	Zeigerer et al., Nature 2012
	Mice	RNAi liver	Rab5 KD leads to loss of the endo-lysosomal system and to the accumulation of glycogen.	Zeigerer et al., Cell Rep 2015
	Mice	RNAi liver	Regulation of Liver Metabolism by the Endosomal GTPase Rab5. Rab5 KD mimics Van Gierke's disease.	Huang et al., PNAS 2001
	3T3-L1 adipocytes	transfected with GFP-Rab5	Rab5 is necessary for GLUT4 internalization.	Tessner et al., Endocrinology 2014
3T3-L1 adipocytes	over expression of SN (DN) mutant	Rab5 Activity Regulates GLUT4 Sorting.	Braccini et al., Nat Comm 2015	
mouse liver	recruitment	PI3K-C2g is a Rab5 effector selectively controlling endosomal Akt2 activation downstream of insulin signalling.		
VPS34 (PI3K)	C. Elegans	RNAi	Alteration of lipid metabolism	Lapierre et al., Curr Biol

	Mice	Vps34 floxed mice	Liver-specific Albumin-Cre;Vps34f/f mice develop hepatomegaly and hepatic steatosis, and impaired protein turnover.	2011 Jaber et al., PNAS 2012 Bilanges et al., Nat Comm 2017
	mice	mutant	Heterozygous Vps34 kinase-dead mice show alterations in cellular energy metabolism, activating the AMPK pathway in liver and muscle.	
Vps15 (PI3K)	C. Elegans	RNAi	Reduction of whole body fat content. Abnormal lipid metabolism	Ashrafi et al., Nature 2003
	hepatocellular carcinoma Hepa1.6 cells; primary hepatocytes; Vps15f/f mice	RNAi	Acute and chronic depletion of hepatic Vps15 increases insulin sensitivity and Akt signalling leading to alleviation of the metabolic syndrome in genetic and diet-induced models of insulin resistance and diabetes.	Nemazany et al., Nat Comm 2015
VPS45	3T3-L1 adipocytes	expression & RNAi	Sorting of GLUT4 into its insulin-sensitive store requires the Sec1/Munc18 protein mVps45.	Roccisana et al., Mol Biol Cell 2013
	skeletal muscle	o/e and RNAi	Conditional deletion of APPL2 in skeletal muscles enhances insulin sensitivity, leading to an improvement in glucose tolerance.	Cheng et al., Diabetes 2014 Prudente et al., Am J Hum Genet. 2015
	diabetic patients	mutants	Loss-of-Function Mutations in APPL1 in Familial Diabetes Mellitus.	
	L6 myoblasts and myotubes, C2C12 myoblasts	o/e and RNAi	APPL1 binds to adiponectin receptors and mediates adiponectin signalling and function.	Mao et al., Nat Cell Biol. 2006
	pancreatic islets	APPL1 KO mice	Deletion of the Appl1 gene leads to impairment of both the first and second phases of insulin secretion.	Wang et al., Diabetologia.

	Rat hepatocytes & liver	o/e and RNAi	APPL1 increases hepatic insulin sensitivity by potentiating insulin-mediated suppression of the gluconeogenic program.	2013 Cheng et al., Cell Metab 2009
	human livers	SNP analysis	Association of Genetic Variation in Adaptor Protein APPL1/APPL2 Loci with Non-Alcoholic Fatty Liver Disease.	Barbieri et al., Plos One 2013
Rab4b	Helicoverpa A.	RNAi	Decrease Glycogen whole body content. Increase the transcription of Foxo	Hou et al., Dev Biol 2012
AP1G1	C. Elegans	RNAi	Reduction of whole body fat content	Webster et al., Cell Rep 2017
Rab35	3T3-L1 adipocytes	o/e of DN Rab35	TBC1D13 is a Rab35 specific gap that plays an important role in Glut4 trafficking in adipocytes.	Davey et al., Traffic 2012
Rab11-FIP3	Drosophila M.	RNAi	Reduction of whole body fat content	Pospisilik et al., Cell 2010
VPS51 (GARP/EARP)	Danio Rerio	Mutant	Defect in glucose homeostasis	Liu et al., Biochim Biophys Acta 2010
VPS54 (GARP)	C. Elegans	RNAi	Reduction of whole body fat content. Abnormal lipid metabolism	Ashrafi et al., Nature 2003
	Mice	spontaneous recessive point mutation in Vps54	The wobbler mouse is associated with a dysregulation of energy metabolism.	Schmitt-John et al., Nat. Genetics 2005; Moser et al., Mol Genet Genomics 2013

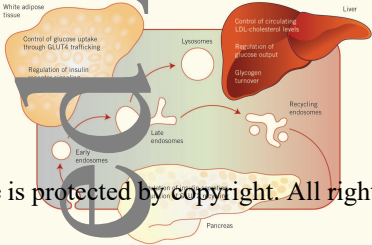
VPS53 (GARP)	mouse and human cell lines & mice	RNAi, Vps54 mutant	The GARP Complex Is Involved in Intracellular Cholesterol Transport.	Wei et al., Cell Rep 2017
COMM D1 (CCC)	Mice	Whole Body KO	Lethal	Van de Sluis B MCB 2007 Vonk et al PlosOne 2011 ;
	Mice	Liver spec. KO	Hepatic copper accumulation and hypercholesterolemia	Bartuzi et al., Nat Comm. 2016 Bartuzi et al., Nat Comm. 2016
	Dogs	Whole Body deficiency	Hepatic copper storage disorder and hypercholesterolemia	
COMM D6 & COMM D9 (CCC)	Mice	Liver spec. KO	Hypercholesterolemia	Fedosei enko et al., Circ Res. 2018
CCDC22 (CCC)	Patients (XLID)	Hypomorphic mutation	Hypercholesterolemia	Bartuzi et al., Nat Comm. 2016
WASH	mouse and human cell lines	RNAi	WASH complex is needed to efficiently recycle the nutrient transporters GLUT1 (also known as SLC2A1) and SLC1A4, and potentially many other surface proteins.	Kvainickas et al., J Cell Sci. 2017
	Patients, Dogs, Liver	Liver spec. KO	CCC- and WASH-mediated endosomal sorting of LDLR is required for normal clearance of circulating LDL.	Bartuzi et al., Nat Comm. 2016
	primary hepatocytes, liver, adipocytes	whole body; liver- and adipocyte-specific Pid1-deficient mice	The adaptor protein PID1 regulates receptor dependent endocytosis of postprandial triglyceride-rich lipoproteins, and whole body glucose homeostasis.	Fischer et al., Mol Metab 2018 ; Chen et al BBA GRM

				(PMID 29391195)
WASHC 1 (WASH)	Mouse embryonic fibroblast Pancreas	KO conditional KO	Impaired LDLR trafficking, reduced LDLR uptake WASH Regulates Glucose Homeostasis by Facilitating Glut2 Receptor Recycling in Pancreatic Beta Cells.	Bartuzi et al., Nat Comm. 2016 Ding et al., Diabetes 2018
WASHC 5 (WASH)	Patients (RSS)	mutation	High plasma LDL-C	Bartuzi et al., Nat Comm. 2016
Retromer complex	human cells 3T3-L1 adipocytes human renal proximal tubule cells (hRPTCs), rat and mouse kidneys.	interaction & infection KD RNAi	PTEN Regulates Glucose Transporter Recycling by Impairing SNX27 Retromer Assembly. VPS35 (retromer) regulates GLUT4 trafficking Loss of renal SNX5 results in impaired IDE activity and insulin resistance in mice.	Shinde et al., Cell Rep 2017 Pan et al., Mol Biol Cell 2017, Yang et al. FASEB J. 2016 Li et al., Diabetologia 2018
COPI	C. Elegans	RNAi	Increase glucose metabolism	Lee et al., Genes Dev 2015
VPS33A /B (CORVET /HOPS)	Drosophila M.	RNAi	Increase of whole body fat content	Baranski et al., PLoS Genet 2018

	Patients	expression/mutation analysis & patient characterization	Patients with Vps33b mutations in the ARC syndrome show cholestasis, metabolic acidosis, nephrogenic diabetes insipidus, chronic diarrhea, platelet abnormalities, and central nervous system anomalies.	Jang et al., J Pediatr Gastroenterol Nutr 2009
	Mice	Vps33b ^{fl/fl} -AlfpCre KO	Vps33b is crucial for structural and functional hepatocyte polarity and defects of lipid metabolism.	Hanley et al., J Hepatology 2017
VPS16 (CORVET/HOPS)	C. Elegans	RNAi	Increase glucose metabolism	Lee et al., Genes Dev 2015
VPS18 (CORVET)	Drosophila M.	RNAi	Reduction of whole body fat content	Baumbach et al., Cell Metab 2014
Rab7	C. Elegans	RNAi	Abnormal lipid metabolism	Ashrafi et al., Nature 2003
	C. Elegans	RNAi	Reduction of whole body fat content	Mukhopadhyaya et al., 2007 ; Ashrafi et al., Nature 2003
	Drosophila M.	RNAi	Reduction of whole body fat content	Baumbach et al., Cell Metab 2014
	hepatic cells	RNAi	The Small GTPase Rab7 as a Central Regulator of Hepatocellular Lipophagy.	Schroeder et al., Hepatology 2015
VPS28 (ESCRT I)	Drosophila M.	RNAi	Increase of whole body fat content	Baumbach et al., Cell Metab 2014

	Drosophila M.	RNAi	Reduction of whole body fat content	Pospisilik et al., Cell 2010
	mouse & monkey	activation through enhanced ubiquitination	Tmbim1 is a multivesicular body regulator that protects against non-alcoholic fatty liver disease in mice and monkeys by targeting the lysosomal degradation of Tlr4.	Zhao et al., Nat Medicine 2017
	mouse and human cell lines	siRNA against ESCRT-0 (STAM1), ESCRT-I (UBAP1), ESCRT-II (Vps22), or ESCRT-III (CHMP4C)	The Endosomal Sorting Complex Required for Transport Pathway Mediates Chemokine Receptor CXCR4-promoted Lysosomal Degradation of the Mammalian Target of Rapamycin Antagonist DEPTOR.	Verma et al., JBC 2015
VPS36 (ESCRT II)	Drosophila M.	RNAi	Increase of whole body fat content	Baumbach et al., Cell Metab 2014
Chmp3 (ESCRT III)	Drosophila M.	RNAi	Increase of whole body fat content	Baumbach et al., Cell Metab 2014
	C. Elegans	RNAi	Reduction of whole body fat content	Ashrafi et al., Nature 2003
	rat adipocytes	DN inhibitor constructs	GLUT4 Traffic through an ESCRT-III-Dependent Sorting Compartment in Adipocytes.	Koumanov et al., Plos One 2012
	mice	promotor analysis	Identification of genetic elements in Chmp3 that are associated with metabolic diseases by high-throughput mouse phenotyping.	Rozman et al., Nat. Comm 2018
Chmp4c (ESCRT III)	C. Elegans	RNAi	Reduction of whole body fat content	Webster et al., Cell Rep 2017

	mouse and human cell lines	siRNA against ESCRT-0 (STAM1), ESCRT-I (UBAP1), ESCRT-II (Vps22), or ESCRT-III (CHMP4C)	The Endosomal Sorting Complex Required for Transport Pathway Mediates Chemokine Receptor CXCR4-promoted Lysosomal Degradation of the Mammalian Target of Rapamycin Antagonist DEPTOR.	Verma et al., JBC 2015
Chmp1 (ESCRT III)	Drosophila M.	RNAi	Increase of whole body fat content	Baumbach et al., Cell Metab 2014
Vps4	Drosophila M.	RNAi	Reduction of whole body fat content	Baumbach et al., Cell Metab 2014
	rat adipocytes	DN inhibitor constructs	GLUT4 Traffic through an ESCRT-III-Dependent Sorting Compartment in Adipocytes.	Koumanov et al., Plos One 2012
VAMP3	C. Elegans	RNAi	Reduction of whole body fat content. Abnormal lipid metabolism	Ashrafi et al., Nature 2003
Exoc6 (Exocyst)	Drosophila M.	RNAi	Reduction of whole body fat content	Baumbach et al., Cell Metab 2014
Rab10	3T3-L1 adipocytes	RNAi	SEC16A is a RAB10 effector required for insulin-stimulated GLUT4 trafficking in adipocytes.	Bruno et al., JCB 2016
	mice	Rab10 KO	The small Rab GTPase, Rab10, is required for insulin-stimulated GLUT4 translocation in cultured 3T3-L1 adipocytes.	Vazirani et al., Diabetes 2016
	3T3-L1 adipocytes	o/e CA Rab10 & RNAi	Rab10, a Target of the AS160 Rab GAP, Is Required for Insulin-Stimulated Translocation of GLUT4 to the Adipocyte Plasma Membrane.	Sano et al., Cell Metab 2007
Munc18c	mice	Heterozygous KO	Altered Glut4 translocation in muscle ; defect of beta-cells insulin secretion; severe glucose intolerance	Oh et al., Diabetes 2005



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