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Lessons from cavin-1 deficiency

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Abstract

Caveolae have been implicated in a wide range of critical physiological functions. In the past decade, the dominant role of cavin-1 in caveolae formation has been established, and it has been recognized as another master regulator for caveolae biology. Human patients with cavin-1 mutations develop lipodystrophy and muscular dystrophy and have some major pathological dysfunctions in fat tissue, skeleton muscle, heart, lung and other organs. Cavin-1 deficiency animal models consistently show similar phenotypes. However, the underlying molecular mechanisms remain to be elucidated. Recent studies have suggested many possible pathways, including mechanosensing, stress response, signal transduction, exosome secretion, and potential functions in the nucleus. Many excellent and comprehensive review articles already exist on the topics of caveolae structure formation, caveolins, and their pathophysiological functions. We will focus on recent studies using cavin-1 deficiency models, to summarize the pathophysiological changes in adipose, muscle, and other organs, followed by a summary of mechanistic studies about the roles of cavin-1, which includes caveolae formation, ribosomal RNA transcription, mechanical sensing, stress response, and exosome secretion. Further studies may help to elucidate the exact underlying molecular mechanism to explain the pathological changes observed in cavin-1 deficient human patients and animal models, so potential new therapeutic strategies can be developed.

Introduction

Caveolae or little caves were first observed by electronic microscopy in the 1950s [1,2]. The first caveolae protein was discovered in the 1990s, named caveolin-1 [3,4]. Subsequently, two other caveolin isoforms (caveolin-2 and 3) were reported [5–7]. In the past decade another family of caveolae proteins, named cavins (cavin-1, 2, 3, and 4) have also been documented (reviewed in [8]). These cavin proteins were originally studied outside of caveolae and named in the context of the experiments being performed. Briefly, cavin-1 was called polymerase I and transcript release factor (PTRF) [9], cavin-2 was called serum deprivation response gene (SDPR) [10] and cavin-3 was called SRBC for SDPR-related gene that binds PKC [11], and cavin-4 was called muscle-related coiled-coil protein [12]. Caveolins and cavins are expressed in some degree of tissue-specific manner [13–19]. The components of caveolae in non-muscle cells include caveolin-1 and caveolin-2 and cavin-1–

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Competing Interests

The author declares that there are no competing interests associated with this manuscript.

3. Caveolin-3 and cavin-4 are expressed only in cardiac and skeletal muscle. Studies from knockout mouse models also demonstrate only caveolin-1 [20,21], caveolin-3 [22], and cavin-1[23] are absolutely necessary for caveolae structure formation.

In 1998, Cavin-1 was first reported as a cofactor of RNA polymerase I (Pol I) in the nucleus [9]. It was subsequently described as a caveolae protein by the Vinten and Tranum–Jensen group from Denmark in 2001 [24]. They isolated a 'lipid raft' fraction from adipocytes, followed by applying a hybridoma antibody screening approach. They identified a clone called '2F11,' that specifically labeled adipocyte caveolae using immunogold staining electron microscopy technique. This antibody recognized a target ~ 60-kDa, so the antigenic protein was initially called 'cav-p60.' The same group confirmed its caveolae-specific expressions in other tissues [25,26], and it has been called 'cavin' since then [27]. Another group used a proteomics approach to locate cavin-1 and its other family members in human adipocyte caveolae and document many key biochemical features [28]. In the past 10 years, studies using cavin-1 deficiency models have helped to established the role of cavin-1 in caveolae biology. In this review, we will summarize the pathophysiological relevance that was learned from these working systems, followed by the insights about the potential cavin-1 dependent molecular and cellular mechanisms that underlie these changes.

Pathophysiological relevance of cavin-1

Cavin-1 in adipocytes: lipodystrophy

One major phenotype found in adult cavin-1 null mice is an abnormal loss of fat (termed lipodystrophy) [23]. The knockout mice developed dramatically reduced adipose tissue throughout the body [23,29] and were resistant to diet-induced obesity; epididymal white fat cells were small and relative insensitive to insulin and β-adrenergic agonists, resulting in dramatically reduced adipocyte lipid storage, lipid tolerance, and lipolysis [29]. This metabolic disorder has also been found in human patients with loss-of-function cavin-1 mutations, which is termed as congenital generalized lipodystrophy type 4 (CGL4) [30–32]. The reduced lipid accumulation in adipocytes was thought to be caused by decreased fatty acid uptake and incorporation and the virtual absence of insulin-stimulated glucose transport [29]. At the molecular level, studies have shown cavin-1 was involved in the regulations of two key enzymes of lipolysis, perilipin and hormone-sensitive lipase (HSL) [29,33]. The phosphorylation of both proteins has been known as key initial steps of lipolysis. Perilipin phosphorylation was impaired in cavin-1 null adipocytes [29]. In the plasma membrane cavin-1 bound to HSL for the regulation of its cellular localization, and loss of cavin-1 caused HSL dislocation [34]. Further functional studies using knockdown and overexpression of cavin-1 suggested the role of cavin-1 in adipocyte lipolysis is dependent on its own phosphorylation as well [33], although the details remain to be determined. Besides cavin-1 phosphorylation, it is possible other mechanisms might be involved in the regulation of lipolysis. One study indicated that acetylated cavin-1 preferentially interacted with HSL and recruited it to the caveolae, thereby promoting lipolysis [35]. Nevertheless, it remains unclear how reduced lipolysis contributes to the lipodystrophy phenotype in cavin-1 deficiency models as one might expect the opposite response to reduced fat cell mass.

Studies also support that there is a close correlative relationship between cavin-1 expression level and adipocyte expansion and lipid storage, although the conclusions from two following reports seem inconsistent. One of the studies shows the increasing density of caveolae accommodates larger lipid droplets and storage with increased adipocyte functionality, and conversely lipid mobilization that induces lipid droplet shrinkage leads to the loss of cavin-1 expression, which is coincident with caveolae disassembly/disappearance [36]. However, another report demonstrated the opposite result: cavin-1 overexpression compromises adipocyte differentiation with decreased lipid storage capacity, and its mRNA levels are positively correlated with cellular senescence and therefore limited expansion in human adipose tissue [37]. This apparent inconsistency is not necessary completely contradictive, since the direct casual or consequence relationship between cavin-1 expression level and adipocyte function has not been firmly established. One also needs to consider the factors involved in the different working systems used at different stages of healthy or diseased states. The role of cavin-1 in physiological healthy adipocyte expansion might be quite different from its function in adipocytes with pathological changes in obesity and metabolic disease conditions.

The role of caveolae and cavin-1 in lipid metabolism has been reviewed elsewhere [18]. In one of our recent studies, we showed that cavin-1 is less significant in adipocyte differentiation or lipolysis signal transduction [38]. However, we believe these were secondary changes due to the loss of growth ability upon nutrient loading. This idea is also supported by the fact that the lipodystrophy phenotype only becomes obvious in adult mice (>6–8 weeks) rather than newborns or infants (unpublished data). In our cavin-1 knockout mice studies [23,29], we saw that the newborn knockout mice looked quite normal and almost identical with wild-type littermates. The loss of fat tissue became increasingly evident as the knockout mice grew older. A similar situation was found in human patients with cavin-1 mutations; almost all reports were about toddlers or children, not newborns [39–42]. These suggest that a direct effect on lipid metabolism (such as lipolysis) may not be the primary mechanism for cavin-1 action. Instead, the functions of cavin-1 in other cellular localization, such as nucleus or cytosol might be the major causes of the lipodystrophy phenotype.

Cavin-1 in muscle: muscular dystrophy

Among cavin family proteins, cavin-4 is the one showing muscle specificity [14,43]. But in this review, we will focus on the findings directly linking cavin-1 to muscle physiology. Human mutations in the cavin-1 gene cause CGL4 associated with myopathy [30]. Long-QT syndrome and fatal cardiac arrhythmia are observed in some patients with CGL4 [44]. Cavin-1 null mice recapitulated these pathological changes, showing impaired exercise ability and muscle hypertrophy with increased muscle fiber size and muscle mass, a compensatory response to muscle weakness and wasting [45]. Skeletal muscles without cavin-1 expression were fibrotic and exhibited impaired membrane integrity accompanied by an apparent compensatory activation of the dystrophin–glycoprotein complex and elevated expression of proteins involved in muscle repair function [45]. One study showed with electron tomography that cavin-1 null muscle fibers had a striking loss of sarcolemmal

organization, aberrant T-tubule structures, and increased sensitivity to membrane tension [46].

Studies also demonstrate an essential role of cavin-1 in the cardiovascular system. A progressive cardiomyopathic phenotype with wall thickening of the left ventricle and reduced fractional shortening were observed in 16-week-old cavin-1 null mice [47]. Further histological analysis revealed cardiomyocyte hypertrophy accompanied by progressive interstitial/perivascular fibrosis [47]. Consistently, another study shows cardiac ejection properties were modestly reduced in cavin-1 knockout mice, along with the exaggeration of intrinsic beating rate, diastolic stiffness and stretch-dependent diastolic and systolic forces as well [48]. Similar to skeleton muscle, the hypertrophy phenotype was also observed in cavin-1 null heart, as the increased right ventricle mass of the heart and elevated right ventricular pressure were reported by another group [49].

Cavin-1 in lung and other tissues

The function of cavin-1 in other tissues has also been examined. Cavin-1-deficient mice exhibited an increased lung tissue density (vessel thickness) and hypertrophic remodeling of pulmonary arteries [49]. Consistent with this, a study showed that cavin-1 deficient mice possessed dramatically altered distal lung morphology and increased lung elastance, which were associated with hypercellularity and accumulation of lung macrophages [50]. The bladder weight in male cavin-1 null mice was increased, with a reduction in depolarization-induced contraction but no change of micturition patterns and diuresis [51].

Overall, the whole-body cavin-1 null mice are not embryonic lethal but do develop some major phenotypes in adipose tissue and muscular organs, including the skeleton, cardiovascular system, and smooth muscle. These data raise questions about the underlying molecular mechanisms that are responsible for these pathological changes.

Molecular and cellular functions of cavin-1

An indispensable role in caveolae formation

The major breakthrough about the function of cavin-1 in caveolae biology came from two groups' studies ~2008, using RNAi knockdown and gene knockout models: knockdown cavin-1 by shRNA in cultured 3T3-L1 adipocyte diminishes caveolin-1 expression [52]; cavin-1 knockdown reduces caveolae density in NIH 3T3 fibroblasts [53]; cavin-1 knockdown via morpholino technology at the stage of zebrafish embryo development shows a dramatic reduction in caveolae [53]; and a whole-body cavin-1 knockout mouse model shows the complete loss of caveolae in fat, skeleton, and smooth muscle tissue, accompanied by diminishing protein expressions of all caveolin isoforms [23]. These results were confirmed by other groups with the same or similar working models [14,54]. Together, these studies well established the essential role of cavin-1 in caveolae formation. So far the dominant roles of cavin-1 and caveolin1/3, two 'master' proteins, are indispensable and well accepted in the field. The phenotypes in cavin-1 null mice almost recapitulate the ones in both caveolin-1 and caveolin-3 null mice, suggesting that a caveolae-dependent mechanism might be important to the dysfunctions observed in cavin-1 null mice. However, caveolin-1

and caveolin-3 null mice both show diminished cavin-1 expression, it is also possible that the phenotypes observed in both knockout mouse models were driven by the function of cavin-1 outside of caveolae.

Cavin-1 positively regulates ribosomal RNA transcription in the nucleus

Cavin-1 was first characterized by its Pol I-related regulatory function ~20 years ago by the Grummt group [9]. Cavin-1 was studied for its role in ribosomal RNA transcription and was called 'Polymerase I and Transcript Release Factor' (PTRF) [9]. Transcription by all three classes of nuclear RNA polymerases includes initiation, elongation, and termination. Termination of Pol I-mediated pre-ribosomal RNA (pre-rRNA) transcription is a two-step process that involves pausing elongating transcription complexes and releasing both pre-rRNA and Pol I from the template. By using a cell-free *in vitro* reconstituted transcription assay system, the authors demonstrated that PTRF not only augments the efficiency of transcript release but also increases the overall rate of transcription in a concentration-dependent manner [9]. More detailed mechanistic studies from the same group revealed that PTRF-mediated transcript disassociation could lead to increasing the efficiency of reinitiation, which was potentially regulated through PTRF-phosphorylation [55,56]. However, the physiological relevance of this activity had never been established in cells or *in vivo*.

Recently, we used a primary mouse and cultured adipocyte experimental systems to show that cavin-1 localized to the nucleus and associated with the Pol I transcription complex, directly affecting metabolically regulated ribosomal DNA transcription [38]. These studies not only show a specific role of cavin-1 on metabolism-regulated ribosomal DNA transcription in the adipocytes but also add another layer of regulation to rDNA transcriptional complexity. This mechanism could explain the lipodystrophy phenotype that was observed in mouse models and human patients lacking functional cavin-1. Considering ribosome biogenesis is a general cellular 'building' process, we believe this cavin-1 dependent ribosome biogenesis mechanism may be applied to explain muscle weakness, growth failure and wasting phenotypes in muscular dystrophy, simply because these could be the result of impairment of protein synthesis.

Cavin-1 in mechanical stress response and membrane remodeling

It is known that caveolae are essential in response to mechanical stress and are involved in the regulation of subsequent membrane remodeling [57]. The mirrored expression levels between caveolin-1 and cavin-1 and their indispensable roles in caveolae formation suggest that cavin-1 must be involved in such regulation. The role of cavin-1 in mechanical stress response was established both *in vitro* and *in vivo* by the following studies. In cultured cells, upon mechanical stress, the interaction between cavelin-1 and cavin-1 was decreased and cavin-1 was disassociated from caveolae [58]. In muscle, caveolae occupied ~s 50% of the sarcolemmal area and were predominantly assembled into rosette shapes, which can also be preferentially disassembled in response to increased membrane tension [46]. Loss of cavin-1 was associated with abnormal sarcolemma organization and T-tubule structures and increased sensitivity to membrane tension, and these resulted in compromised muscle integrity [46]. Mechanistically this can be explained through various downstream targets or

pathways. Cavin-1 could act as a docking protein for MG53, which has been believed to be an essential component of the membrane repair machinery [59]. Cells that do not express endogenous cavin-1 show defective trafficking of MG53 to membrane injury sites [60]. Our recent studies show that upon insulin stimulation, cavin-1 can be acutely translocated to focal complex compartments, where it regulates focal complex formation through an interaction with paxillin [61]. We also found that loss of cavin-1 impairs focal complex remodeling and focal adhesion formation and causes a mechanical stress response, concomitant with activation of proinflammatory and senescence/apoptosis pathways [61]. The mechanical stress response is closely related to cell volume change. Considering the dramatic change of adipocyte size under different metabolic conditions, this cavin-1-dependent mechanical sensing mechanism likely plays a significant role in the regulation of adipocyte lipid storage. Additionally, cell migration is another biological process that requires significant membrane remodeling. Many studies have suggested cavin-1 is involved in this process [62–66]. One of the studies demonstrates cavin-1 can suppress tumor cell migration through the inhibition of focal adhesion dynamics [64].

Cavin-1 in response to oxidative stress and p53 pathway activation

There are many reports that suggest there might be a connection between cavin-1 and stress responses that were caused by cellular genotoxic and oxidative insults. Cavin-1 expression was up-regulated in stressed cells, such as senescent human fibroblasts [67], cells with oxidative stress induced by hydrogen peroxide [68], and cells with diabetes-induced oxidative stress [69]. Hypoxia can reduce its expression in 3T3-L1 adipocytes [70]. A recent study showed evidence that cavin-1 and other family members can physically interact with p53 in the cytosolic compartment [71]. These studies indicate that cavin-1 may directly link stress to the gene transcriptional changes through p53-dependent pathways. Besides the direct interactions between cavins and p53, our studies show that cavin-1-dependent ribosomal RNA transcription contributes to the activation of the p53 pathway through an indirect ‘ribosomal or nuclear’ stress mechanism [38]. Nevertheless, all the data consistently support that cavin-1 might be involved in a p53 pathway-related stress response. As a well-known master regulator, p53 plays significant roles in cell senescence, growth arrest, and apoptosis (reviewed in [72,73]), which are also the common characteristics that can be observed in lipodystrophy and muscular dystrophy. This cavins-p53 stress sensing and response pathway might serve as a common mechanism mediating the pathological changes in adipose tissue and other tissues, such as muscle.

Cavin-1 in secretory pathway and exosome secretion.

There are some recent reports suggesting that cavin-1 may be involved in the secretory pathway. One study using prostate cancer cells (PC-3) showed that cavin-1 can reduce the secretion of a subset of proteins, including proteases, cytokines, and growth regulatory proteins [74]. Another study suggested when the newly synthesized Fam198a precursor (a member of secreted protein kinase family [75]) in the endoplasmic reticulum (ER) was transported to the Golgi apparatus, in which it cleaved into the secreted mature form, cavin-1 was required for Fam198a secretion after its maturation in the Golgi apparatus [75]. Although the exact underlying mechanism remains unclear, it is possible cavin-1 dependent

caveolae biogenesis could indirectly impact on protein secretion pathway and the disruption of caveolae system will affect the secreted proteins' functions.

Other studies also show cavin-1 overexpression increased exosome secretion and stimulated cell growth both *in vitro* and *in vivo* [76]. Moreover, cavin-1 itself can be found in human plasma, and is, at least in part, carried by exosomes [77]. However, more studies are needed to clarify how cavin-1 is involved in exosome secretion.

Summary/future directions

As illustrated in Figure 1, multiple functions of cavin-1 at a various subcellular location (plasma membrane, cytosol, and nucleus) could mediate the pathological changes of lipo- and muscular dystrophies that were observed in cavin-1 null mice. However, the precise molecular mechanism(s) remains to be determined in future studies. Cavin-1 undergoes many post-translational modifications, such as phosphorylation, ubiquitination, and acetylation. It will be interesting to see how cavin-1 acting as a signaling molecular mediates the upstream signal(s) to downstream effects. Such research would expand our understandings of caveolae biology.

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Abbreviations

CGL4	congenital generalized lipodystrophy type 4
ER	endoplasmic reticulum
HSL	hormone-sensitive lipase
Pol I	polymerase I
pre-rRNA	pre-ribosomal RNA
PTRF	polymerase I and transcript release factor
SDPR	serum deprivation response gene

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Perspectives

- *Importance of the field*: Human patients with loss of function in cavin-1 suffer from lipodystrophy and muscular dystrophy. However, the precise molecular actions of cavin-1 remain unclear.
- *Current thinking*: Cavin-1 is indispensable in caveolae formation and involved in ribosomal RNA transcription, mechanical stress response, oxidative and other cellular stress response, exosome and secretion, and many others that are related to caveolae.
- *Future directions*: Results from current studies suggest that cavin-1 might serve as a signaling molecule that integrates nutrients, mechanical stress, oxidation, and other signals with systemic transcriptional regulation. Further studies are needed to address the molecular details (such as multiple post-translational modifications of cavin-1) that are responsible for these functions.

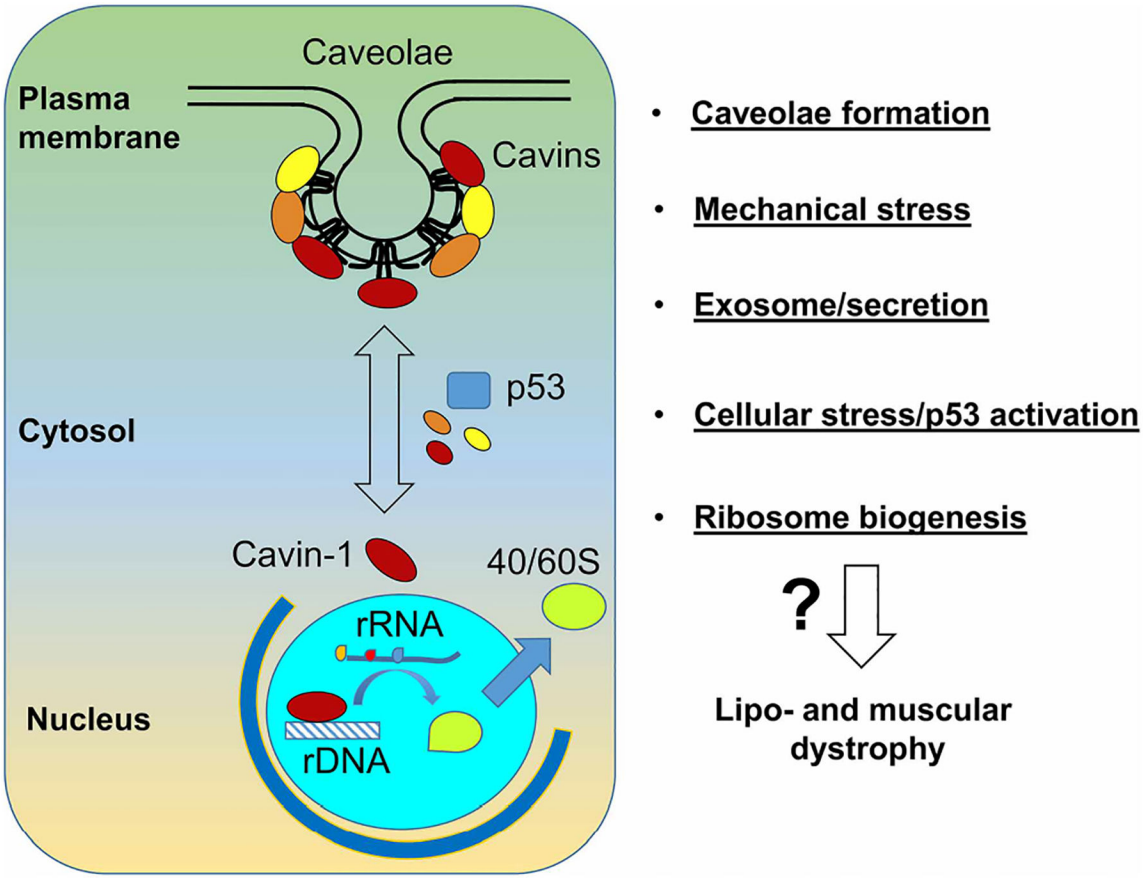

Figure 1. Potential molecular mechanisms for the pathological changes observed in cavin-1 deficiency.

Cavin-1 plays a critical role in caveolae formation. It also has functions in other cellular locations, such as nucleus and cytosol (left panel). Current studies have suggested it is involved in many important cellular processes (right panel). Further research is needed to elucidate which one(s) are responsible for the lipodystrophy and muscular dystrophy phenotypes.