THE CAVEOLIN-2 – FROM CELL BIOLOGY TO MEDICINE

KAWEOLINA 2 – OD BIOLOGII KOMÓRKI DO ZNACZENIA PROGNOSTYCZNEGO W MEDYCYNIE

Zuzanna PODEMSKA-JEDRZEJCZAK[1], Agnieszka MALIŃSKA[1], Monika ŚWIERCZEWSKA[1], Bartłomiej PEREK[2], Michał NOWICKI[1]

[1]Department of Histology and Embryology, Poznan University of Medical Sciences, Poland
[2]Department of Cardiac Surgery, Poznan University of Medical Sciences, Poland

Summary: Caveloae are essential membrane structures that play a role in intracellular transport, signalling and the maintenance of cholesterol equilibrium. Caveolin-2 is one of the major proteins involved in the formation of caveolae whose roles remain unclear. In this review we gather the present knowledge about this protein as well as the different mechanisms it is thought to play a role in, from its involvement in proliferation regulation mechanisms to its putative role in different cancers. Caveolin-2 seems to have a more predominant role than previously thought and is probably responsible for many functions that was first thought to be driven by caveolin-1. This indicates that the understanding of this protein is crucial in the context of cell signalling and intracellular transport.

Key words: caveolin-2, caveolae, caveolin-1

Streszczenie: Kaweole są podstawowymi strukturami błon komórkowych uczestniczącymi w transporcie wewnątrzkomórkowym, przekazywaniu sygnałów oraz utrzymaniu równowagi cholesterolu. Kaweolina 2 jest jednym z głównych białek uczestniczących w formowaniu kaweoli, jednak jej rola nie została jeszcze dobrze poznana. Praca stanowi przegląd aktualnej wiedzy na temat kaweoliny 2 oraz szeregu procesów w których odgrywa rolę – począwszy od regulowania aktywności proliferacyjnej komórek aż po przypuszczalny udział w procesie nowotworzenia. W ostatnich latach kaweolina-2 budzi zainteresowanie licznych zespołów badawczych i wydaje się być bardzo prawdopodobnym, że rola tego białka w utrzymaniu homeostazy na poziomie komórki jest znacznie większa niż sądzono w latach 90-tych. Niewykluczone jest, że posiada ona wiele funkcji przypisywanych pierwotnie kaweolinie 1. Z tego też powodu usystematyzowanie aktualnej wiedzy na temat kaweoliny 2 oraz jej roli w transporcie wewnątrzkomórkowym i procesach przekazywania sygnałów wydaje się być uzasadnione.

Słowa kluczowe: kaweolina 2, kaweole, kaweolina 1

INTRODUCTION

Discovered in the early 50s among the first structures observed by electron microscope, caveolae, which means « small caves », are flask shape invaginated (or wide-opened craters) structures of 50-100nm in diameter visible in the plasma membrane [2, 46]. They are present in most mammalian cell types like adipocytes, fibroblasts, epithelial and smooth muscle cells. They can represent up to 50% of the plasma membrane surface in endothelial cells [30]. Studies suggest that the role of caveolae is explained through three non-exhaustive models. First, caveolae may function as scaffolds for signalling events; secondly, as intracellular transport vesicles; and finally, as a buffer which helps to regulate plasma membrane lipid composition and fatty acid incorporation [18]. For a long time it was believed that caveolae formation was exclusively dependent on the presence of proteins called caveolin, but recently it was found that a complex of regulatory proteins, called cavins play a crucial role in the formation of the whole structure [2].

Caveolins are the integral membrane proteins which have been the major defining markers of caveolae. They are small proteins of 18-24 kD, but an interesting and significant fact is that they can form oligomeric complexes (14-16 monomers) [46]. Caveolins are the principal components of the caveolae and are highly integrated into caveolae function. However, according to recent studies, caveolin proteins can have roles in the regulation of cellular activities which are not related to caveolae. These additional roles include lipid transport, gene expression, and mitochondrial function. These caveolae-independant functions may occur by way of their presence in other cellular membranes, such as: the Golgi apparatus, the endoplasmic reticulum, exocytic and endocytic vesicles, the nucleus, mitochondria and lipid droplets [38, 46]. They are expressed ubiquitously in mammals, but their expression levels vary considerably between tissue [5, 46]. Three caveolins have been identified so far, called respectively caveolin-1 (Cav-1), caveolin-2 (Cav-2) and caveolin-3 (Cav-3). Cav-1 and Cav-2 are present in a wide range of cells, like endothelial cells, adipocytes, fibroblasts and smooth-muscles cells, Cav-3 has been found to be present only in skeletal and cardiac muscle. Cav-2 is colocalized and coexpressed with Cav-1, and requires its presence for proper membrane localization [5, 46].

The cavins belong to cytoplasmic proteins family that together with caveolins participates in caveolae formation and function. The cavin group consists of four members: cavin-1 (also known as polymerase I and transcript release factor, PTRF), cavin-2 (also known as serum deprivation response protein, SDPR), cavin-3 (also known as serum deprivation response factor-related gene product that binds to C-kinase, SRBC), and cavin-4 (also known as muscle-restricted coiled-coil protein,

MURC) [30]. These proteins have mainly a scaffolding role but also regulate the availability of caveolins. They share two specific domains, a leucine zipper-like domain (involved in protein-protein interactions) and a PEST domain (involved in protein turnovers), as well as a phosphorylation motif. Overall cavins are involved in regulation of caveolae formation and modulate the function of caveolins [2]. Despite all that is already known in the network of mechanism involving the formation of caveolae, the role of Cav-2 remains poorly understood, whether regarding the involvement of caveolae formation or not.

CAVEOLIN-2 – GENE ORGANISATION

Cav-2 is a small integral protein weighing about 20 kD and is a major component of the inner surface of caveolae. Cav-2 is co-localized and co-expressed with Cav-1, and requires its presence for proper membrane localization [5, 46]. Unlike Cav-1 and Cav-3, Cav-2 alone is insufficient to drive the formation of morphologically identifiable caveolae [49]. Cav-2 and Cav-1 are similar in many aspects, but differ regarding their functional domains, particularly regarding the G-protein binding domain and caveolin scaffolding domain [49]. Moreover, the role of Cav-2 is linked to its localisation, meaning the type of cell or tissue[42].

Cav-2 protein is coded from a gene (*Cav-2*) present on human chromosome 7q31.1. This 8941 nucleotides long gene shares around 60% of similarity with the two others members of the human caveolin gene family, *Cav-1* and *Cav-3*. Human *Cav-2* and *Cav-1* are present on the same chromosome and are only distanced by 19kb, which could be related to the fact that *Cav-2* is co-expressed with *Cav-1* [46].

On an organizational level, it is interesting to notice that the last exon of *Cav-1* and *Cav-3* is present in two parts separated by an exon in *Cav-2* gene (fig. 1). It is believed that this last exon contains most of the functional domains of the protein [14]. On the other hand, these three genes share particular amino-acid sequences, like the one present in the hydrophilic amino-terminal domain, called «caveolin signature motif » [13]. The importance of Cav-2 is supported by the fact that the *Cav-2* gene is conserved from worms to humans [36].

Cav-2 is generating 3 different isoforms by alternative splicing: *Cav-2α* (the most abundant isoform [35]), *Cav-2β* and the lesser known *Cav-2γ* [8].

Cav-1 and *Cav-2* have been shown to be expressed in similar tissues, which is consistent with the fact that their protein form stable hetero-oligomeric complex. The tissue distribution of Cav-2 mRNA is extremely similar to Cav-1 mRNA. This mRNA are indeed found in such cell type as endothelial cells, smooth muscle cells, skeletal myoblasts, fibroblasts and adipocytes [36].

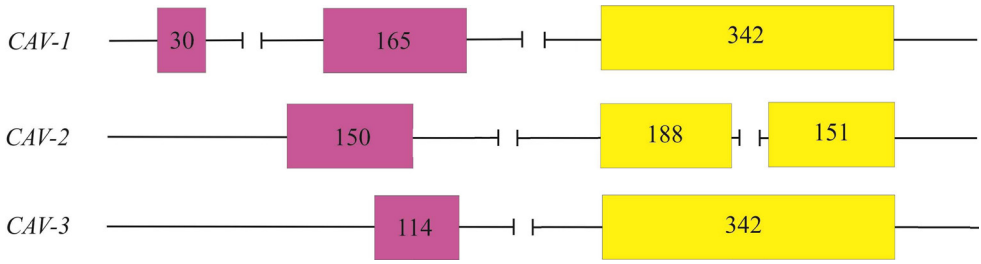

FIGURE 1. Schematic depiction of gene organization in caveolin gene family. Color-coded boxes represent the respective correspondence between exons. Numbers within each box refer to the number of nucleotides, according to [6]

CAVEOLIN-2 – PROTEIN STRUCTURE

Caveolin's structure can be described by three regions: a hydrophilic cytosolic N-terminal domain, a membrane spanning region and a hydrophilic C-terminal domain. Both the membrane-spanning region and the C-terminal domain are thought to be associated with the membrane, due to the presence of S-acylation on three cysteine residues [37].

Human Cav-2 is a 54-72 residues protein. It differs from Cav-1 and Cav-3 by the phosphorylation on Tyr19, Ser23 & Ser36, respectively by the tyrosine kinase Src and the casein kinase II for the serines residues (fig. 2) [19].

The signature sequence of amino acids, characteristic of the caveolin family, is represented by the presence of a 33-amino acid membrane-spanning segment and a hydrophilic 43- to 44-amino acid C-terminal domain. Cav-2 has the specificity to have its N-terminal domain shorter of 26 amino acids than Cav-1α [37].

Cav-1 and Cav-2 have been shown to form a stable complex of 200-400 kD *in vivo*, even if the presence of Cav-2 is neither necessary nor sufficient for the formation of caveolae. Interestingly caveolae invagination resulting from the coexpression of Cav-1 and Cav-2 are deeper [24]. On the other hand, Cav-2 may be also expressed in cell depleting Cav-1, which suggest that their co-expression is not mandatory [36]. In this case Cav-2 is detected as mixture of monomers and dimers that are retained for example in the Golgi complex or lipid droplets [33]. The interaction between Cav-1 and Cav-2 is thought to occur by the participation of both membrane-spanning domains. Moreover, the caveolin scaffolding domain (CSD) is probably playing a crucial role in this interaction. Cav-2 was thought to be unable to form complexes with Cav-3, making the interaction between Cav-1 and Cav-2 an isoform-specific interaction [8], but there are studies providing the evidence that hetero-oligomers between Cav-2 and Cav-3 can occur in muscle cells, for example cardiomyocytes [33].

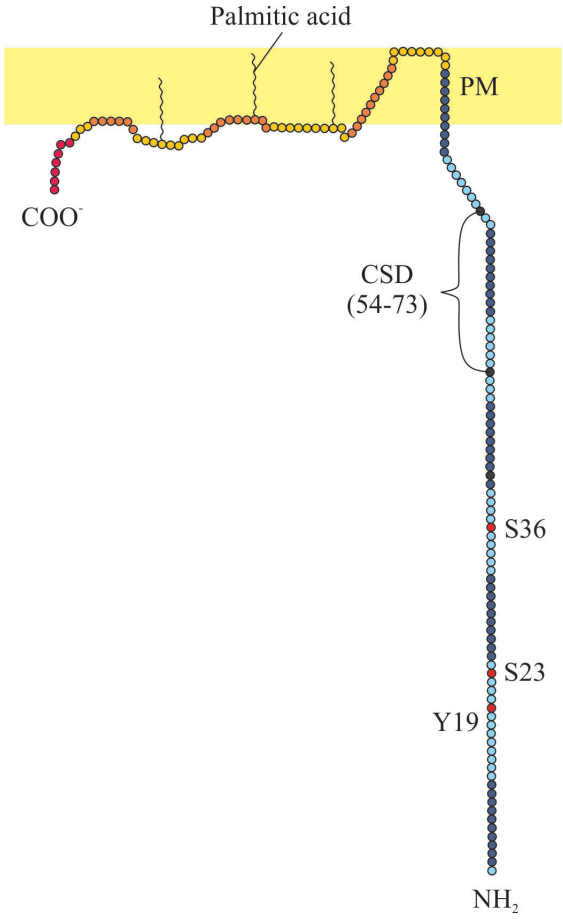

FIGURE 2. Schematic representation of caveolin-2. Phosphorylation of Ser23, Ser36 and Tyr19 is represented on this model of the 162 amino-acids protein. **CSD** – Caveolin Scaffolding Domain involved in different functions of the protein; **OD** – Oligomerization Domain involved in oligomers formation, according to [18]

CAVEOLIN-2 – CELL LOCALISATION

Cav-2 synthesis occurs in the rough endoplasmic reticulum (RER), adopting an unusual hairpin configuration, having the N- and C- terminal domains exposed to the cytoplasm [2]. In order to exit the RER, the COOH-terminal segment from residue 120-150 is required [17]. Cav-2 is then matured in the Golgi apparatus, like other caveolins. The co-expression with Cav-1 is necessary for Cav-2 to exit the Golgi apparatus and to migrate to the submembrane area of the cell [2].

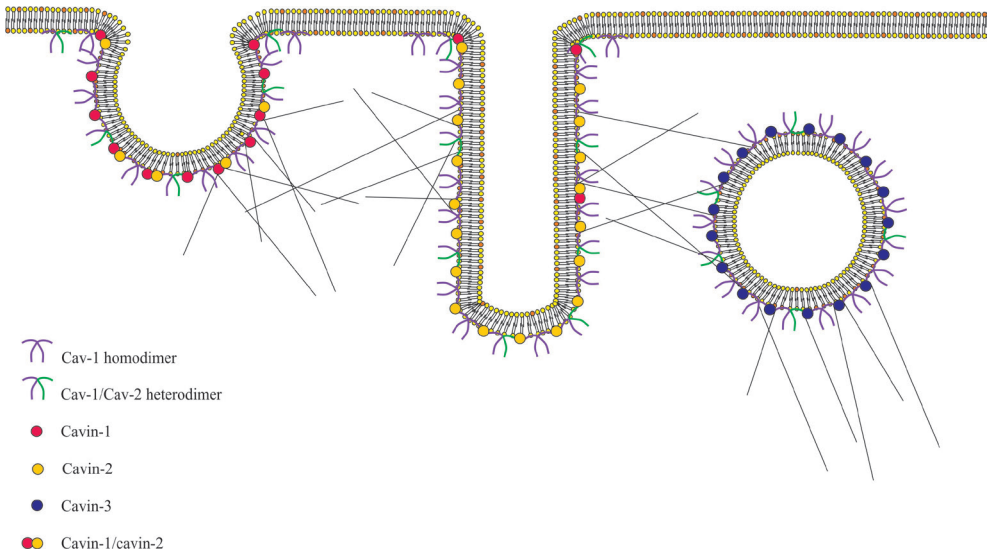

FIGURE 3. Schematic representation of different caveolae structures. Dimers of Cav-1 and Cav-2 (violet and green lines) form the backbone of caveolae. Cavins finalize invagination. Cavin-1 (red circle) is responsible of normal flask-shaped caveolae, alone or by interaction with cavin-2 (combined red and yellow circles). Cavin-2 in certain conditions form elongated caveolae involved in channel formation. Cavin-3 (blue circles) form vesicle from caveolae. Dark lines represent cytoskeletal components mediating the interaction between cavins and caveolins, according to [5]

Some hetero-oligomers of Cav-1 and Cav-2 are already formed in the RER. These hetero-oligomers can also be found into trans-Golgi vesicles, like basolateral vesicles. During their biosynthesis, caveolin oligomers increase in size on their pathway to the cell surface. Thanks to interaction with Cav-1, Cav-2 is undertaking changes from a soluble endoplasmic reticulum form to an insoluble post-Golgi form, and in the meantime is modified by the addition of increasing numbers of phosphate groups, which results in the increasing size of the whole complex. Then, hetero-oligomers are incorporated into the basolateral transport vesicles among the trans-Golgi network (TGN) [29]. The NH_2-terminal segment, residues 70-86, is required to attach to the membrane when reaching it [17].

Phosphorylation of specific serine has an impact in the localization of Cav-2. A 23-phosphorylated Cav-2, in the presence of Cav-1, would be preferentially localized in the plasma membrane. On the other hand, a 36-phosphorylated Cav-2 would be primarily found in intracellular perinuclear regions. Serine 23 phosphorylation induce the targeting of Cav-2 to plasma membrane caveolae in epithelial cells and especially in endothelial cells [43]. The state of phosphorylation of Cav-2 (on Ser-23 and Ser36) is also essential to contribute to Cav-1-dependent invaginated caveolae formation [44].

Some studies showed that Cav-2, especially its β isoform could be directed to the surface of lipid droplets (LD), which may be found not only in adipose cells cytoplasm, but also in many other cells, for example in the foam cells which play a crucial role in the atherosclerotic plaques formation [17]. In this case three domains are essential to allow the localization in the LD: the central hydrophobic domain (residues 87-119), the NH_2-terminal domain (residues 70-86) and the COOH-terminal domain (residues 120-150) [17].

CAVEOLIN-2 – FUNCTIONS

Exact functions of Cav-2 remain so far unclear, even if several studies highlight different roles this protein could have. General studies have shown that the absence of Cav-2 had no impact on the presence of Cav-1. Moreover, the lack of Cav-2 has no incidence in trafficking or in caveolae formation [32]. This leads to the idea that Cav-2 acts, among other things, as a regulatory protein for Cav-1.

In addition to plasma membrane caveolae, Cav-2 can exist in other subcellular compartments such as RER, Golgi apparatus, cytosolic vesicles, lipid droplets, mitochondrium or nucleus [4, 16]. This support the idea that Cav-2 may play different roles depending on its localization and has tissue and cell-specific functions [43].

The observation of Cav-2 deficient mice leads to the hypothesis of the role Cav-2 plays in lung architecture and function, as these mice display pulmonary defects, like hyperproliferation of endothelial cells and thickening of alveolar septa [49]. Moreover, wild type Cav-2 is highly expressed in this organ, strengthening this hypothesis. Deeper analysis allowed to understand that this protein had a role in the control of endothelial cells proliferation. Interestingly, this role has been observed to be both an inhibition of anti-proliferation, and an inhibition of proliferation; for example in the case of mouse lung endothelial cells (MLECs) [42, 47, 48]. The anti-proliferation inhibition has been more thoroughly studied and is related to the transforming growth factor beta (TGF-β) [42, 48]. The phosphorylation of different amino-acids of Cav-2 affects this regulation. Particularly the phosphorylation of the N-terminal tyrosine seems to be essential for this process, as the N-terminal serine phosphorylation plays a minor role in this case [1]. Tyrosine phosphorylated-Cav-2 remained associated with caveolae [43]. Overall, the ambiguous role of Cav-2 in the regulation of proliferation of endothelial cells seems to depend on the context of the cell, Cav-2 can act as a molecular switch avoiding disproportional response of anti- and pro-proliferation signals [42,48].

Another function of Cav-2 that was observed is related to its GTPas activating protein (GAP)-like activity [37]. The difference in the nucloetidic sequence level with Cav-1 impacts the role of the two translated proteins related to G proteins inactivation [37]. Cav-2 will act as a GAP, inactivating the G-proteins and recruiting them in

caveolae membranes, when Cav-1 acts as a Guanosine nucleotide dissociation inhibitor (GDI) and keeps G-proteins inactive [37, 49].

Cav-2 may be also involved in other mechanisms. Some studies mention an involvement of this protein in lipid metabolism, with a regulating role, as the absence of the protein increases the risk of obesity and type 2 diabetes [49]. A fat-rich diet may increase or decrease the expression of Cav-2, depending on the length of feeding, but Cav-2 always behaves in the opposite way to Cav-1. Obesity is a nutritional disorder which is caused by a prolonged imbalance between calorie intake and its consumption. This disorder is linked to different metabolic alterations such as type 2 diabetes mellitus or hyperinsulinaemia, and associated with health threats like atherosclerosis, hypertension or immune impairment [3, 10]. Obesity is often related to insulin resistance. The function of Cav-2 in cell cycle regulation was therefore examined in human insulin receptor-overexpressing rat-1 fibroblast (Hirc-B) *in vitro* cells, in which treatment with insulin induced Cav-2 gene expression in a time-dependent manner [21, 49]. Interestingly Hirc-B cells do not seem to express Cav-1, which suggest that caveolae are absent in these cells. Due to lack of Cav-1, Cav-2 has to be localized in noncaveolar intracellular compartments [43].

Under certain conditions, Cav-2 can be also found in LD, especially in its β isoform. Overexpressed Cav-2 may be accumulated not only in the Golgi apparatus but also in LD of transiently transfected Fischer rat thyroid (FRT) cells [28]. This LD targeting suggests that Cav-2 can play a role in lipid storage or even lipid metabolism [43].

Also, Cav-2 alteration may be linked to some kinds of cancer, as the sequence of this protein is localized in a fragile site (FRA7G) which is often deleted in human cancers [49]. For example, the absence of Cav-1 is linked to the development of prostate cancer [45], and Cav-2 can promote tumor growth. Its expression is also increased in breast cancer [12, 34].

Cav-2 has been shown to be a potential good predictor of internal thoracic artery (ITA) grafts patency rate. Study participants developing ITA graft occlusion within 24-month period after CABG (coronary artery bypass grafting) expressed Cav-2 within smooth muscle cells of tunica media, which was exclusively located within mitochondrial matrix and cristae. The presence of Cav-2 in this tissue is rarely reported, but in the rare occasion when this protein is present, it is recognized as the factor involved in stress adaptation by preserving membrane structure and mitochondrial function [15, 26]. Therefore the presence of Cav-2 in mitochondria of smooth muscle cells of ITA grafts may reflect the systemic body status in terms of chronic stress. ITA graft occlusion may not result from Cav-2 expression within smooth muscle cells but most probably follows systemic disorders involving a wide imbalance between the factors damaging and repairing the cells. This supports the idea that immunohistochemical estimation of Cav-2 presence within the muscle cells of tunica media in ITA transplants might indicate the risk of graft failure [26].

TABLE 1. Cellular localization of caveolin-2, role and specific original references

CELLULAR LOCALIZATION	ROLE OF CAVEOLIN-2	REFERENCES
Plasma membrane caveolae	Signal transduction	[9], [37], [25]
Mitochondria	Lipid transport Metabolic regulation Preserve function	[15], [26]
Lipid droplets	Lipid transport	[28], [31]
Golgi apparatus	Lipid transport	[7], [28]
Endoplasmic reticulum	Lipid transport	[41], [40]
Secretory pathway vesicles	Endocytosis Exocytosis Transcytosis	[11], [39], [27]
Nucleus	Gene regulation Tumor supressor	[20], [23], [22]

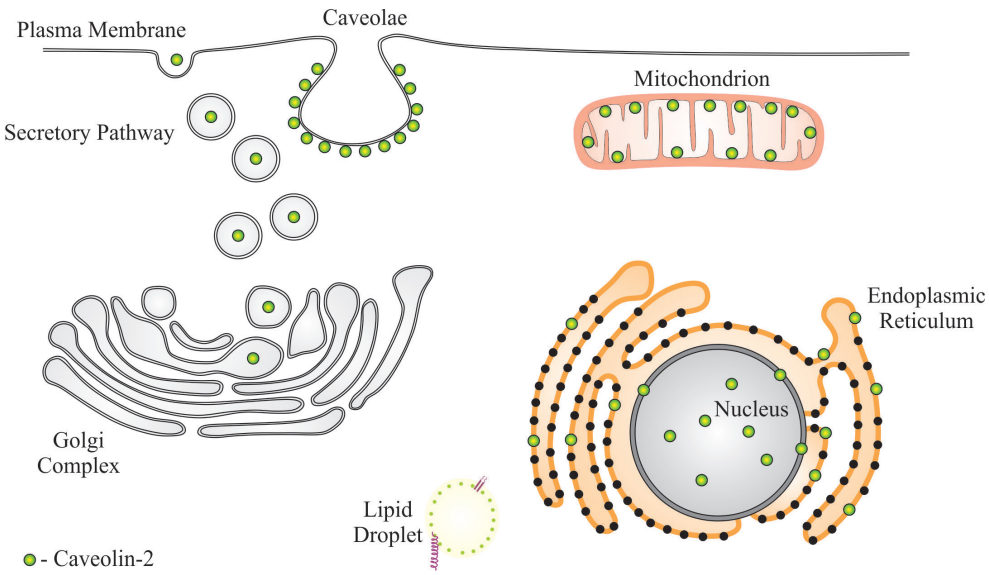

FIGURE 4. Caveolin-2 is localized into multiple cellular compartments. Localization of caveolin-2 is depicted into various intracellular organelles to regulate a number of cellular processes, according to [16]

CONCLUSION

Among the proteins participating in the formation of caveolae, Cav-2 remains the one which functions are the most unclear. Despite its structural similarities to Cav-1, it seems that its role may be not only complementary but sometimes radically different, depending on the tissue or the type of cell where Cav-2 is localized. The presence of Cav-2 in cells in which caveolae are absent supports the fact that this particular protein may have a role unrelated to caveolae formation and can also be regarded as proliferation regulatory protein. This suggests a need to rethink the significance of this protein, which can globally play a more important role than originally thought, being responsible for functions which were previously thought to be restricted to Cav-1. These new functions are of significant interest as they can be linked to different important diseases like obesity or cancer, and therefore help to diagnose them earlier. Cav-2 can also be used as a marker to help predict rejection in the case of ITA grafts.

Recent discoveries about Cav-2 lead to the idea that this protein's roles were underestimated and further studies are necessary to confirm the hypothetic functions already suggested and explore possible new functions yet to be uncovered.

ACKNOWLEDGMENTS

This publication is part of "Project WroVasc – Integrated Cardiovascular Centre", co-financed by the European Regional Development Fund, within Innovative Economy Operational Program, 2007-2013 realized in Regional Specialist Hospital, Research and Development Center in Wroclaw. "European Funds – for the development of innovative economy"

REFERENCES

[1] Abel B, Willoughby C, Jang S, Cooper L, Xie L, Vo-Ransdell C, Sowa G: N-terminal tyrosine phosphorylation of caveolin-2 negates anti-proliferative effect of transforming growth factor beta in endothelial cells. *FEBS Lett*., 2012; **586**: 3317-3323.

[2] Bastiani M, Parton RG: Caveolae at a glance. J Cell Sci, 2010; **123**: 3831-3836.

[3] Bray GA: The epidemic of obesity and changes in food intake: the Fluoride Hypothesis. *Physiol. Behav.,* 2004; **82**: 115-121.

[4] Caravia L, Dudau M, Gherghiceanu M, Tanase C, Enciu AM: Could caveolae be acting as warnings of mitochondrial ageing? *Mech. Ageing Dev*., 2015; **146-148**: 81-87.

[5] Chidlow JH, Sessa WC: Caveolae, caveolins, and cavins: complex control of cellular signalling and inflammation. *Cardiovasc. Res.*, 2010; **86**: 219-225.

[6] Cohen AW, Hnasko R, Schubert W, Lisanti MP: Role of caveolae and caveolins in health and disease. *Physiol. Rev.*, 2004; **84**: 1341-1379.
[7] Conrad PA, Smart EJ, Ying YS, Anderson RG, Bloom GS: Caveolin cycles between plasma membrane caveolae and the Golgi complex by microtubule-dependent and microtubule-independent steps. *J. Cell Biol.*, 1995; 131: 1421-1433.
[8] Couet J, Belanger MM, Roussel E, Drolet MC: Cell biology of caveolae and caveolin. *Adv. Drug Deliv. Rev.*, 2001; **49**: 223-235.
[9] Couet J, Li S, Okamoto T, Ikezu T, Lisanti M: Identification of Peptide and Protein Ligands for the Caveolin-scaffolding Domain implications for the interaction of caveolin with caveolae-associated proteins. *J. Biol. Chem.*, 1997; **272**: 6525-6533.
[10] Das M, Gabriely I, Barzilai N: Caloric restriction, body fat and ageing in experimental models. *Obes. Rev*., 2004; **5**: 13-19.
[11] Di Guglielmo GM, Le Roy C, Goodfellow AF, Wrana JL: Distinct endocytic pathways regulate TGF--beta receptor signalling and turnover. *Nat. Cell Biol.*, 2003; **5**: 410-421.
[12] Elsheikh SE, Green AR, Rakha EA, Samaka RM, Ammar AA, Powe D, Reis-Filho JS, Ellis IO: Caveolin 1 and Caveolin 2 are associated with breast cancer basal-like and triple-negative immunophenotype. *Br. J. Cancer*, 2008; **99**: 327-334.
[13] Engelman JA, Zhang X, Galbiati F, Volonte D, Sotgia F, Pestell RG, Minetti C, Scherer PE, Okamoto T, Lisanti MP: Molecular genetics of the caveolin gene family: implications for human cancers, diabetes, Alzheimer disease, and muscular dystrophy. *Am. J. Hum. Genet.*, 1998; **63**: 1578-1587;
[14] Fra AM, Pasqualetto E, Mancini M, Sitia R: Genomic organization and transcriptional analysis of the human genes coding for caveolin-1 and caveolin-2. *Gene,* 2000; **243**: 75-83.
[15] Fridolfsson HN, Kawaraguchi Y, Ali SS, Panneerselvam M, Niesman IR, Finley JC, Kellerhals SE, Migita MY, Okada H, Moreno AL, Jennings M, Kidd MW, Bonds JA, Balijepalli RC, Ross RS, et al.: Mitochondria-localized caveolin in adaptation to cellular stress and injury. *FASEB J.* Off. Publ. Fed. Am. Soc. Exp. Biol., 2012; **26**: 4637-4649.
[16] Fridolfsson HN, Roth DM, Insel PA, Patel HH: Regulation of intracellular signaling and function by caveolin. *FASEB J.*, 2014; **28**: 3823-3831.
[17] Fujimoto T, Kogo H, Ishiguro K, Tauchi K, Nomura R: Caveolin-2 Is Targeted to Lipid Droplets, a New "Membrane Domain" in the Cell. *J. Cell Biol*., 2001; **152**: 1079-1086.
[18] Hansen CG, Nichols BJ: Exploring the caves: cavins, caveolins and caveolae. *Trends Cell Biol.,* 2010; **20**: 177-186.
[19] Head BP, Insel PA: Do caveolins regulate cells by actions outside of caveolae? *Trends Cell Biol.*, 2007; **17**: 51-57.
[20] Jeong K, Kwon H, Lee J, Jang D, Hwang EM, Park JY, Pak Y: Rab6-mediated retrograde transport regulates inner nuclear membrane targeting of caveolin-2 in response to insulin. *Traffic Cph. Den.*, 2012; **13**: 1218-1233.
[21] Kim S, Pak Y: Caveolin-2 regulation of the cell cycle in response to insulin in Hirc-B fibroblast cells. *ResearchGate*, 2005; **330**: 88-96.
[22] Kwon H, Jeong K, Hwang EM, Park JY, Hong SG, Choi WS, Pak Y: Caveolin-2 regulation of STAT3 transcriptional activation in response to insulin. *Biochim. Biophys. Acta*, 2009; **1793**: 1325-1333.
[23] Kwon H, Jeong K, Hwang EM, Park JY, Pak Y: A novel domain of caveolin-2 that controls nuclear targeting: regulation of insulin-specific ERK activation and nuclear translocation by caveolin-2. *J. Cell. Mol. Med.,* 2011; 15: 888-908.
[24] Lahtinen U, Honsho M, Parton RG, Simons K, Verkade P: Involvement of caveolin-2 in caveolar biogenesis in MDCK cells. *FEBS Lett.*, 2003; **538**: 85-88.
[25] Li S, Couet J, Lisanti MP: Src tyrosine kinases, Galpha subunits, and H-Ras share a common membrane-anchored scaffolding protein, caveolin. Caveolin binding negatively regulates the auto-activation of Src tyrosine kinases. *J. Biol. Chem*., 1996; **271**: 29182-29190.

[26] Malińska A, Podemska Z, Sujka-Kordowska P, Witkiewicz W, Nowicki M, Perek B, Witt M: Caveolin 2: a facultative marker of unfavorable prognosis in long-term patency rate of internal thoracic artery grafts used in CABG. Preliminary report. Interact.
[27] , 2016; 1-7.
[28] Minshall RD, Sessa WC, Stan RV, Anderson RGW., Malik AB: Caveolin regulation of endothelial function. *Am. J. Physiol. – Lung Cell. Mol. Physiol.*, 2003; **285**: L1179-L1183.
[29] Ostermeyer AG, Paci JM, Zeng Y, Lublin DM, Munro S, Brown DA: Accumulation of Caveolin in the Endoplasmic Reticulum Redirects the Protein to Lipid Storage Droplets. *J. Cell Biol.,* 2001; **152**: 1071-1078.
[30] Parolini I., Sargiacomo M, Galbiati F, Rizzo G, Grignani F, Engelman JA, Okamoto T., Ikezu T, Scherer PE, Mora R, Rodriguez-Boulan E, Peschle C, Lisanti MP: Expression of caveolin-1 is required for the transport of caveolin-2 to the plasma membrane. Retention of caveolin-2 at the level of the golgi complex. *J. Biol. Chem.*, 1999; **274**: 25718-25725.
[31] Parton RG, del Pozo MA: Caveolae as plasma membrane sensors, protectors and organizers. *Nat. Rev. Mol. Cell Biol.,* 2013; **14**: 98-112.
[32] Pol A, Martin S, Fernandez MA, Ferguson C, Carozzi A, Luetterforst R, Enrich C, Parton RG: Dynamic and Regulated Association of Caveolin with Lipid Bodies: Modulation of Lipid Body Motility and Function by a Dominant Negative Mutant. *Mol. Biol. Cell*, 2004; **15**: 99-110.
[33] Razani B, Wang XB, Engelman JA, Battista M, Lagaud G, Zhang XL, Kneitz B, Hou H, Christ GJ, Edelmann W, Lisanti MP: Caveolin-2-Deficient Mice Show Evidence of Severe Pulmonary Dysfunction without Disruption of Caveolae. *Mol. Cell. Biol.*, 2002; **22**: 2329-2344.
[34] Rybin VO, Grabham PW, Elouardighi H, Steinberg SF: Caveolae-associated proteins in cardiomyocytes: caveolin-2 expression and interactions with caveolin-3. *Am. J. Physiol. – Heart Circ. Physiol.*, 2003; **285**: H325-H332.
[35] Sagara Y, Mimori K, Yoshinaga K, Tanaka F, Nishida K, Ohno S, Inoue H, Mori M: Clinical significance of Caveolin-1, Caveolin-2 and HER2/neu mRNA expression in human breast cancer. *Br. J. Cancer,* 2004; **91**: 959-965;
[36] Scheiffele P, Verkade P, Fra AM, Virta H, Simons K, Ikonen E: Caveolin-1 and -2 in the exocytic pathway of MDCK cells. *J. Cell Biol.*, 1998; **140**: 795-806.
[37] Scherer PE, Lewis RY, Volonte D, Engelman JA, Galbiati F, Couet J, Kohtz DS, van Donselaar E, Peters P, Lisanti MP: Cell-type and tissue-specific expression of caveolin-2. Caveolins 1 and 2 co-localize and form a stable hetero-oligomeric complex in vivo. *J. Biol. Chem*., 1997; **272**: 29337-29346.
[38] Scherer PE, Okamoto T, Chun M, Nishimoto I, Lodish HF, Lisanti MP.: Identification, sequence, and expression of caveolin-2 defines a caveolin gene family. *Proc. Natl. Acad. Sci. U. S. A.,* 1996; **93**: 131-135.
[39] Schilling JM, Patel HH.: Non-canonical roles for caveolin in regulation of membrane repair and mitochondria: implications for stress adaptation with age. J. Physiol., 2016; **594**: 4581-4589.
[40] Schubert W, Frank PG, Razani B, Park DS, Chow CW, Lisanti MP: Caveolae-deficient endothelial cells show defects in the uptake and transport of albumin in vivo. *J. Biol. Chem*., 2001; **276**: 48619-48622.
[41] Smart EJ, Ying YS, Donzell WC, Anderson RG: A role for caveolin in transport of cholesterol from endoplasmic reticulum to plasma membrane. *J. Biol. Chem.*, 1996; **271**: 29427-29435.
[42] Smart EJ, Ying YS, Conrad PA, Anderson RG: Caveolin moves from caveolae to the Golgi apparatus in response to cholesterol oxidation. *J. Cell Biol.*, 1994; **127**: 1185-1197.
[43] Sowa G: Caveolae, caveolins, cavins, and endothelial cell function: new insights. *Front. Physiol*., 2012; **2**: 120.
[44] Sowa G: Novel Insights into the Role of Caveolin-2 in Cell- and Tissue-Specific Signaling and Function. *Biochem. Res. Int*., 2011; **2011**: e809259.
[45] Sowa G, Pypaert M, Fulton D, Sessa WC: The phosphorylation of caveolin-2 on serines 23 and 36 modulates caveolin-1-dependent caveolae formation. Proc. Natl. Acad. Sci., 2003; **100**: 6511-6516.

[46] Sugie S, Mukai S, Yamasaki K, Kamibeppu T, Tsukino H, Kamoto T: Significant Association of Caveolin-1 and Caveolin-2 with Prostate Cancer Progression. *Cancer Genomics – Proteomics*, 2015; **12**: 391-396.
[47] Williams TM, Lisanti MP: *The caveolin proteins. Genome Biol*., 2004; **5**: 214.
[48] Xie L, Frank PG, Lisanti MP, Sowa G: Endothelial cells isolated from caveolin-2 knockout mice display higher proliferation rate and cell cycle progression relative to their wild-type counterparts. *Am. J. Physiol. – Cell Physiol*., 2010; **298**: C693-C701.
[49] Xie L, Vo-Ransdell C, Abel B, Willoughby C, Jang S, Sowa G: Caveolin-2 is a negative regulator of anti-proliferative function and signaling of transforming growth factor-β in endothelial cells. *Am. J. Physiol. – Cell Physiol.*, 2011; **301**: C1161-C1174.
[50] Zhu L luan, Cui Y, Chang Y sheng, Fang F de: A Second Protein Marker of Caveolae: Caveolin-2. *Chin. Med. Sci. J*., 2010; **25**: 119-124.

Editor – Maciej Zabel

Received: 06.12.2016
Accepted: 07.01.2017
Zuzanna Podemska-Jedrzejczak
Department of Histology and Embryology, Poznan University of Medical Sciences
Swiecickiego 6 St., 60-781 Poznań, Poland
tel.:(4861)854-64-58
fax: (4861)854-64-40
e-mail: zpodemsk@ump.edu.pl