Caveolae: From Cell Biology to Therapeutic Strategies

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Summary

Caveolae, special microdomains within the plasma membrane, were discovered in 1950s. Morphologically, they are "flask-shape" plasma membrane invagination. The caveolar system is composed of specific lipids, cholesterol and sphingolipids, and variety of protein molecules. The caveolin protein was later identified as a marker protein for caveolae. It has been shown that caveolae and caveolin implicate in a wide range of physiological and pathological conditions. They play roles in modulating lipid homeostasis, regulating signal transduction pathway and vesicular trafficking. They also have been involved in pathogenesis of many human diseases. Further understanding of the caveolae and caveolin cell biology will gain more insight into human physiology and pathology, leading to a very potential therapeutic strategy.

Keywords: Caveolae; Caveolin; Caveolar system; Plasma membrane microdomain

Introduction

The lipid bilayer of plasma cell membrane is composed mainly of phospholipid, cholesterol, other lipids and various proteins. Recently, it has been known that the plasma membrane compositions are not evenly distributed but rather are organized into more specific microdomains. For example, the clathrin-coated pits are well characterized to be a specific domain for endocytosis or intracellular junction (Roth, 2006). In the past fifty years, caveolae were discovered and have been continuously explored among those specific components of the plasma membrane microdomains. Caveolae were first described in 1953 in the heart endothelial cells by Palade, calling them plasmalemmal vesicles (Couet et al., 2001; Stan, 2005). In 1955, Yamada described similar structure in the gall bladder epithelial cells, naming caveolae intracellulares according to their "little carve-like " structures (Couet et al., 2001; Stan, 2005).

The caveolae membrane system comprises of unique lipid and proteins. Caveolin was first identified as a signature protein only found in caveolae (Anderson, 1998). Since the discovery of the caveolae and caveolin, it has been shown that they play important roles in a wide range of signal transduction processes affecting both physiological and pathological conditions, such as lipid and cholesterol homeostasis, vascular diseases, tumor suppression, and bacterial infection (Razani et al., 2002). Their roles are vastly different depending on caveolin subtypes and cell types. The gained knowledge and understanding of caveolae membrane system has increased and it is clear now that they implicate in variety of human normal functions and diseases. This review focuses on current knowledge of caveolae and their potential implication to clinical therapeutic strategies.

Morphology of caveolae

Caveolae are classically described as flask-shaped plasma membrane invaginations with a diameter of ~ 50-100 nm in size, however the definition of caveolae has expanded to include vesicles detached from the membrane, groups of caveolae in grape-like structures and a fused form in a shape of a tube (Smart et al., 1999). Caveolae can be found at the plasma membrane of numerous cell types. They are abundant in adipocytes, smooth muscle cells, type I pneumocytes, fibroblasts, lung epithelial cells and endothelial cells (Razani et al., 2002). In some tissues such as lung, caveolae can occupy up to 70% of the alveolar plasma membrane areas (Razani et al., 2002). Caveolae are composed of lipids, which are mainly cholesterol and sphingolipids (glycosphingolipid and sphigomyelin) and several minor lipids including ganglioside, ceramide, diacylglycerol

and phosphatidylinositol, whereas non-caveolar regions are composed primarily of phospholipids (Fielding & Fielding, 2000). Caveolae share biochemical properties with lipid rafts, small platforms composed of sphingolipids and cholesterol (Figure 1). The unusual lipid composition of lipid rafts/caveolae imparts a property that make them resistant to detergent solubilization (Brown & London, 1997). The simple and most commonly used method to separate them from all other cellular constituents is by purification with nonionic detergent such as Trition X-100 at 4 ^{o}C (Brown & London, 1997). However, caveolae and lipid rafts are not entirely the same. Certain proteins preferentially partition into lipid rafts or caveolae but not both (Razani et al., 2002) and specific signaling mechanisms may occur either in lipid rafts or in caveolae (Sowa et al., 2001). Caveolins are the defining protein components of caveolae which distinguish them from lipid rafts (Okamoto et al., 1998). Caveolin polymerization forms the flask-shaped caveolar invagination and they facilitate the formation of caveolae through their interactions with cholesterol (Smart et al., 1999). Recently, studies from mice deficient in caveolins showed the lack of caveolae (Drab et al., 2001; Simons & Ehehalt, 2002). Caveolae-like domains and caveolins can also be found within the Golgi apparatus, and these reflect the dynamic trafficking of caveolae and caveolins between intracellular compartment and plasma membrane (Dupree et al., 1993; Gkantiragas et al., 2001).

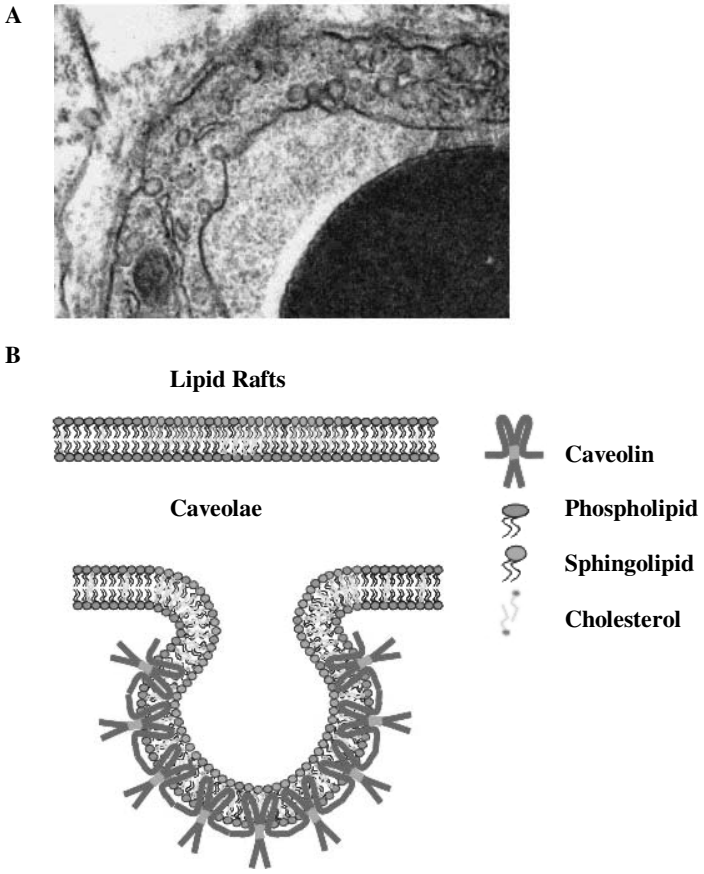

Figure 1 Caveolae structure and caveolin protein (A) Electron micrograph of an endothelial cell showing caveolae, 50-100 nm structures that are either direct invaginations or in close proximity to the plasma membrane. (B) Diagram comparing the biochemical composition of lipid rafts and caveolae lipid rafts form via a coalescence of cholesterol and sphingolipids; as a result, these microdomains have vastly different biochemical properties than the bulk phospholipid bilayer. Caveolae are generally considered to be "invaginated" lipid rafts primarily due to an enrichment in a family of proteins known as the caveolins. Here, the caveolin oligomer is depicted as a dimer for simplicity. (Modified from Razani et al., 2002).

Caveolin proteins

Caveolins are a family of 21-25 kDa integral membrane proteins. Caveolin-1 was first identified as a tyrosine-phosphorylated protein (Stan, 2005). It was also identified by different research group as vesicular integral protein of 21 kDa (VIP 21), an integral membrane protein component of *trans*-Golgi derived transport vesicles (Stan, 2005). Therefore, caveolins not only serve as structural component of caveolae but also have roles in vesicular trafficking and oncogenesis (Liu et al., 2002). Three caveolins are identified in mammalian cells: caveolin-1, caveolin-2 and caveolin-3 (Smart et al., 1999). Most tissues in the body express at least one of those isoforms. Caveolin-1 and -2 are ubiquitously expressed. Adipocytes, endothelial cells, pneumocytes and fibroblast have high levels of caveolin-1 and -2 (Smart et al., 1999). The expression of caveolin-3 is limited to muscle cells (i.e., skeletal, cardiac and smooth muscle cells.) (Smart et al., 1999). Interestingly, most of the cells expressing caveolin-1 do not have caveolin-3, indicating that the two proteins might have different functions in vivo (Liu et al., 2002). It has been shown that caveolins primarily form oligomeric complexes; caveolin-1 homo-oligomeric (Sargiacomo et al., 1995; Song et al., 1997) or caveolins-1 and -2 hetero-oligomeric complexes (Scherer et al., 1997). These oligomeric complexes of caveolins contribute to caveolar formation and their strong detergent-resistant properties (Sargiacomo et al., 1995). Both the N-and C-termini of caveolin are cytoplasmic (Dupree et al., 1993), suggesting an incomplete hairpin structure of caveolins with the putative membrane-spanning domain of the protein (Razani et al., 2002). The C-terminal membrane attachment domain targets caveolin to the *trans*-Golgi and the N-terminal membrane attachment domain specifically directs caveolin to plasma membrane (Razani et al., 2002).

Caveolar biogenesis

It has been demonstrated that cholesterol is crucial for caveolar biogenesis (Simons & Ehehalt, 2002). Cholesterol is served as a spacer between the hydrocarbon chains of the sphingolipids and functions as dynamic glue that keeps the caveolar platform assembly together. If the cell is treated with cholesterol binding agents such as nystatin, filipin, or cyclodextrin, the carveolar membrane system will be completely depleted (Stan, 2005). The intracellular cholesterol levels also affect the biogenesis of other types of plasma membrane microdomains; clathrin-coated pit and synaptic vesicles in a different aspect to caveolae. In mammalian cells, the caveolae is first assembled in the Golgi complex while cholesterol and sphingolipids are synthesized in the endoplasmic reticulum (ER). There is an increasing concentration of cholesterol and sphingolipids from the ER to the Golgi complex where the first assembled caveolae take place then to the plasma membrane (Stan, 2005). Cholesterol and sphingolipids are toxic and their cellular concentrations are tightly limited by the network regulation of cholesterol biosynthesis, the cellular uptake and efflux. Disturbances of these tightly control of cholesterol and sphingolipid lead to variety of lipid and metabolic diseases (Schwencke et al., 2006). The signature protein of caveolae is the caveolin. Several studies have demonstrated that the caveolin-1 transforms the morphology of plasma membrane into flask-shaped caveolae. The caveolin-1 binds to cholesterol and sphingolipid with high binding affinity (Stan, 2005). The caveolin oligomeric complexes contribute to membrane invagination (Couet et al., 2001). Caveolin-1 expression in cells lacking caveolae can induce caveolar formation. The knockout mice lacking carveolin-1 and caveolin-3 have confirmed the importance of these proteins on caveolar formation (Stan, 2005). The cells from caveolin knockout mice do not have any caveolae. Therefore, both critical concentrations of cholesterol and sphingolipids and caveolins provide the appropriate lipid-protein microenvironment for the production of caveolar membrane system.

Functions of caveolae/caveolin in physiological conditions

Caveolae and caveolin proteins have been shown to have numerous roles since their discovery in 1950s. Although some functions of caveolar system have not yet concluded, studies of their roles have been attributed continuously.

Vesicular transport

It is now clear that caveolae and caveolin play an important role in vesicular transports (i.e. transcytosis, endocytosis) (Razani et al., 2002). Caveolae were first hypothesized to function in transcytotic process as a general transporter to uptake protein from luminal side of the endothelial cell to the interstitial compartment. The direct evidence for this function was demonstrated by the specific labeling antibody to the luminal domain of proteins in the endothelial cell caveolae (Schnitzer, 2001). *In situ* experiment showed that these labeling antibodies are able to move rapidly and completely from luminal to apical side through caveolae (Schnitzer, 2001; Simionescu et al., 2002). Caveolae also function in endocytotic processes. Internalization and vesiculation of caveolae have been demonstrated to be distinct from clathrin-mediated endocytosis. For example, ligand internalization by caveolae is significantly slower by 2-4 folds. In addition, the cholesterol binding agent, filipin inhibits the internalization of caveolae but has no effect on clathrin-mediated endocytosis (Parton et al., 1994). Several molecules and certain receptors have shown to be transported by caveoale rather than clathrin-coat pits. Cholera, tetanus toxins, alkaline phosphatase, folate receptors are among other molecules that has been evidentially to be localized and transported via caveolae (Parton et al., 1994). It has been suggested that the GTPase dynamins regulate the caveolar internalization process (Smart et al., 1999). Several components used for general vesicle formation, docking and fusion are concentrated in caveolae and associated with caveolin-1 (Schnitzer et al., 1995). Therefore, caveolae contain the machinery molecules and the same mechanism used in the trafficking to transport cargo from the plasma membrane to internal compartment of the cells.

Cellular lipid homeostasis

Caveolae, caveolin protein and cholesterol have relationship in many aspects. As mentioned above, cholesterol depletion by treating the cell with cholesterol binding agents would destroy caveolar structure. It has been shown that the expression of caveolae in the plasma membrane, the caveolin expression and caveolin mRNA levels are sensitive to free cholesterol concentration of the cell (Fielding & Fielding, 2000). In addition, caveolin-1 can directly form a complex with cholesterol (Couet et al., 2001). The cellular-free cholesterol content is associated with other cholesterol containing molecules in the lipid metabolic pathway, especially a low density lipoprotein (LDL) and a high density lipoprotein (HDL). An increase in extracellular LDL levels results in an increase in free cholesterols and also the expression of caveolae and caveolins in many cell types (Fielding & Fielding, 2000). In contrast, a decrease in free cholesterol by cholesterol-pre-β-migrating HDL, a cholesterol acceptor from the cell in plasma, leads to reductions in caveolae, caveolin as well as caveolin mRNA levels (Fielding & Fielding, 2000). Effects of related network pathways of lipid metabolism on caveolar system have not yet been demonstrated conclusively and are more likely to be complicated. For example, the balance of free cholesterol and cholesterol ester in HDL depends on a scavenger receptor B1, the activity of lecitin:cholesterol acyltransferase, the replacement of free cholesterol from LDL and the transfer of cholesterol ester to other lipoproteins (Fielding & Fielding, 2000).

Intracellular transport of the de novo cholesterol is associated with caveolar system. Cholesterol is synthesized in ER and transported rapidly to plasma membrane, which contains majority of cellular cholesterol. However, less is known about the molecular machinery and

trafficking pathway of the newly synthesized cholesterol transport. Studies using radiolabeled acetate, a precursor of cholesterol biosynthesis, showed that the new cholesterols are distributed to caveolar invaginated membrane via a protein complex, containing caveolins-1 and several chaperone proteins of the heat shock protein families (Uittenbogaard et al., 1998). Based on many observations, cholesterol has high affinity to caveolin-1, therefore this protein may function as one of the cholesterol carriers. Caveolin-1 and intracellular cholesterol levels do have direct relationship. Studies obtained by transfecting cell with caveolin cDNA to upregulate caveolin expression showed an increase of caveolar cholesterol level and free cholesterol efflux (Liu et al., 2002). Contrarily, the cell transfected with antisense caveolin cDNA decreased caveolin expression and free cholesterol efflux (Frank et al., 2001).

Signal transduction

Caveolae are involved in the compartmentalization of various signaling pathways and enriched in molecules that play roles in intracellular signal transduction (Okamoto et al., 1998). The compartmentalization of signal transduction molecules has distinct advantages as it provides a mechanism for the regulation of subsequent signaling events and helps explain "cross-talk" phenomenon between different signaling pathways. Caveolae and caveolar-like domains contain G-protein coupled receptors (i.e., B2, ETA, endothelin, m2 muscarinic), heterotrimeric G proteins, receptor tyrosine kinases, components of the Ras-mitogen-activated protein (MAP) kinase, Src family tyrosine kinases, protein kinase (PK) A and C, and nitric oxide synthase enzymes (see Table 1 for list of caveolae localized proteins) (Okamoto et al., 1998; Razani et al., 2002; Smart et al., 1999). Caveolins function as scaffolding proteins to organize and/or modulate signaling molecules in caveolae (Okamoto et al., 1998). The 20-amino acid peptide corresponding to residues 82-101 of caveolin-1, the so-called caveolin scaffolding domain (CSD), interacts with and negatively regulates the activity of heterotrimeric G-proteins (Li et al., 1995). Other studies show that CSD also inhibits activities of c-Src or Fyn tyrosine kinase (Li et al., 1996). and serine/threonine kinases such as PKA and PKC (Couet et al., 1997; Oka et al., 1997). The CSD of caveolin-1 is capable of binding different types of molecules, thereby it has to recognize a specific motif in order to mediate its action. By using a fusion protein containing CSD to screen a peptide phage display library, CSD-binding motifs have been characterized as having the following sequence: ΦxΦxxxxΦ and ΦxxxxΦxxΦ, where Φ is phenylalanine, tyrosine or tryptophan and x is any residue (Couet et al., 2001; Smart et al., 1999). All molecules that interact with caveolin have at least one CSD-binding motif in their sequences (Couet et al., 2001). It has been shown that most signaling molecules bound to caveolins are inactive (Liu et al., 2002). The function of caveolins in the signaling cascade is mainly to downregulate signal transmission. For example, caveolin-1 directly interacts with endothelial nitric oxide synthase (eNOS) through the CSD (Garcia-Cadeña et al.,1997; Ju et al., 1997). The interaction between eNOS and caveolin-1 inhibits eNOS enzyme activity and this inhibition can be reversed by calcium-calmodulin (Michel, Feron, Sacks et al., 1997; Michel, Feron, Sase et al., 1997). Therefore, caveolin acts as a negative regulator for eNOS in basal conditions to protect the cell from undesired release of nitric oxide (NO) in response to fluctuations of intracellular calcium. The other nitric oxide synthase isoforms, neuronal nitric oxide synthase (nNOS) and inducible nitric oxide synthase (iNOS) contain a similar CSD-binding motif (Garcia-Cadeña et al., 1997). The colocalization of iNOS and caveolin-1 was shown in human colon carcinoma cells and caveolin-1 could down regulate iNOS activity by increasing degradation of the enzyme in the proteasome (Felley-Bosco E et al., 2000).

Table 1 Examples of caveolae localized and caveolin-interacting molecules*

Caveolae localization	Caveolin interaction
G-protein coupled receptors	
β1 and β2 adrenergic receptor	+
Bradykinin B2 receptor	
Endothelin typeA	
Muscarinic2 receptor	
Adenosin A1 receptor	
Membrane proteins	
Insulin receptor	+
Platelet derived growth factor (PDGF) receptor	+
Epidermal growth factor (EGF) receptor	
Vascular epidermal growth (VEGF) receptor	
P-glycoprotein	+
L-type Calcium channel	
Membrane-type 1 matrix metalloproteinase	
Apolipoprotein E receptor 2	
Non-receptor tyrosine and serine/ threonine kinases	
Extracellular regulated kinase (ERK)	
Janus kinase 2 (JAK2)	
Mitogen extracellular kinase (MEK)	
Protein kinase A	
Protein kinase C	
Phosphatidylionositol 3-kinase	
Ras effector serine/threonine kinase (Raf)	
Src family (Src, Fyn, Lyn, Yes)	
Signal transducer and activation of transcription 3 (STAT3)	
Enzymes	
Adenylyl cyclase	+
Endothelial nitric oxide synthase	+
Phospholipase D2	+
Prostacyclin synthase	+
Cyclooxygenase-2	+
Structure proteins	
Actin	
Annexin II	
Dynamin	
Soluble N-ethylmaleimide-sensitive fusion protein attachment protein receptors (SNAREs)	
Synaptosomal protein (SNAP)	

Note.
*Modified from Razani et al.(2002)

Caveolae/caveolin in pathological conditions (human diseases)

In spite the roles of caveolae and caveolins in physiological conditions, they have implicated in pathogenesis of various human diseases. Recently, a number of studies of carveolar system in a variety of pathological conditions have gained rapidly and this knowledge contributes the potential implications to therapeutic strategies.

Cancer

Cell proliferation and differentiation are two fundamental cellular processes for normal tissue development and homeostasis. Caveolin-1 has been shown to inhibit cellular proliferation (Williams & Lisanti, 2005) and it may play a role in transformation and tumorigenesis. It has

been demonstrated that human caveolin-1 gene was located on the position in the chromosome frequently deleted in a variety of human cancers, including breast, ovarian, colon, prostate and renal carcinomas (Williams & Lisanti, 2005; Williams et al., 2004). For instance, a decrease of caveolin-1 expressions was found in breast, lung, and ovarian carcinomas (Williams et al., 2004). Moreover, the caveolin-1 knockout mice had the formation of breast tumor followed by the progression of mammary tumor and lung metastasis (Williams et al., 2004). These observations show that caveolin-1 has tumor suppressor characteristics. However, the expression pattern of caveolin-1 is controversial depending on the tumor cell types. In contrast, some studies indicate a tumor promoting effect of caveolin-1 (Williams & Lisanti, 2005). The overexpression of caveolin-1 was demonstrated in prostate carcinomas and event further upregulated in metastasis (Williams et al., 2005). In gastrointestinal cancers, the role of caveolin-1 is more divergent; it is reduced in human colon carcinoma cell lines, but it is increased in esophageal squamous cell carcinoma (Bender et al., 2000; Kentaro Kato et al., 2002). All these data confirm roles of caveolin-1 in cell transformation and carcinogenesis, although a specific function of caveolin-1 in different cancers still needs further investigation. Recently, studies showed possible roles of caveolin-2 and -3 in carcinogenesis as well (Carver & Schnitzer, 2003). Another potential contribution of caveolin in cancer is the role in process of angiogenesis (Bauer et al., 2005). The study of caveolin knockout mice and the *in vitro* data of antisense oligonucleotides shows that angiogenesis is decreased markedly when caveloins are absent from the endothelial cells (Bauer et al., 2005).

Vascular proliferative disease

The pathogenesis of vascular proliferative diseases involves atherosclerosis and restenosis. Atherogenesis is characterized by an altered endothelial function, a decrease of the vasodilator nitric oxide (NO), a recruitment of mononuclear leukocytes to the intima, a proliferation of vascular smooth muscle cells and a production of extracellular macromolecules. Caveolae and caveolin-1 are present in almost every cell types that are implicated in the development of atherosclerosis, including endothelial cells, vascular smooth muscle cells and macrophages (Li et al., 2005; Mineo & Shaul, 2006). They regulate the signal transduction pathways that play roles in these diseases. Caveolin-1 overexpression prevented cell proliferation of vascular smooth muscle cells (Li et al., 2005). In endothelial cells, caveolin-1 formed a complex with an eNOS enzyme and had an inhibitory effect, resulting in a decrease of NO production (Fleming & Busse, 1999). The appropriate amounts of NO from the endothelial cells prevent the early step of plaque formation (Zimmermann et al., 2002). The disturbance of caveolin-eNOS complex leads to an increase in NO production that would be one of a therapeutic strategy for atherosclerotic prevention. The statins, a group of drugs used in treatment of hypercholesterolemia and prevention of atherosclerosis, are able to disrupt the caveolin-1-eNOS complex by reduction of caveolin-1 expression in response to decreased cholesterol synthesis (Endres, 2006).

Insulin signaling and diabetes

Diabetes mellitus is characterized by hyperglycemia with groups of common metabolic disorders. Most diabetic patients develop and suffer from microvascular diseases (i.e. retinopathy and diabetic renal failure) and macrovascular diseases (i.e. coronary artery and cerebral vascular diseases). The type 2 diabetes is preceded by insulin resistance, in which the action of insulin and/or insulin receptor is impaired in adipose tissues and skeletal muscles (Cline et al., 1999). Caveolae and caveolin-1 have been demonstrated to play a role in insulin receptor signaling (Campbell et al., 2001). Insulin receptors contained the caveolin-binding motif where the scaffolding domain of caveolin-1 and -3 directly interacted with, resulting in stimulation of receptor activity (Yamamoto et al., 1998). In addition, the depletion of membrane cholesterol in adipose cells

caused a significantly reduced response to insulin stimulation (Yamamoto et al., 1998). Taken together of caveolin-1 and insulin receptor modulation, it is reasonable to propose that the caveolin-1 scaffolding domain peptides or peptide mimics may be one of the target therapeutic molecules in the management of type II diabetes although more investigation in clinical levels are needed.

Muscular dystrophy

The muscular dystrophy is a heterogeneous group of myopathies characterized by progressive muscle degeneration and replacement with fibrous connective tissue. Duchenne muscular dystrophy, an X-linked recessive disorder, is the most common and severe form of muscular dystrophy. The genetic defect is caused by the absence or mutant production of dystrophin, a protein expressed in skeletal, myocardium and smooth muscle cells. The dystrophin forms complex with several molecules including caveolin-3 in caveolae (Smart et al., 1999). Genetic evidence using transgenic mice to overexpress caveolin-3 shows that these mice developed phenotypes of muscular dystrophy: loss of skeletal muscle dystrophin, muscle fiber necrosis and connective tissue infiltration (Schwencke et al., 2006). The muscular dystrophy patients showed the mutation of cytoplasmic domain of caveolin-3 (Campbell et al., 2001). To date, several point mutations and a deletion of caveolin-3 gene have been characterized and are responsible for other distinct phenotypes of autosomal muscular dystrophy such as distal myopathy (Campbell et al., 2001). The current method to overcome some of clinical symptoms of the muscular dystrophy is the effective delivery recombinant DNA constructs of dystrophin gene to produce the proteins (Schwencke et al., 2006). The delivery of caveolin-3 antisense oligonucleotides to block its expression might be another therapeutic option to improve the clinical symptoms.

Infections

Pathogens including viruses, parasites and bacteria have complicated mechanisms in invading host cells in order to survive and replicate as well as avoiding host defense. The different routes used by these pathogens affect the pathogenesis. Several pathogens enter to the human host cells via the clathrin-coated pit endocytosis (Roth, 2006). Classically, the translocation of the endocytotic vesicle moves to lysosome, which contains acidic environment for protein degradation. The pathogens are capable of avoiding destruction within lysosome by preventing fusion with lysosome or preventing acidification within the lysosomal compartment (Pizarro-Cerda & Cossart, 2006). After the discovery of caveolae and lipid raft microdomains, it has been demonstrated that some pathogens also used caveolae to achieve entry into the host cells (Shin & Abraham, 2001; Zaas et al., 2005). A variety of bacteria, bacterial toxins, and viruses have mechanisms of entry into the host cell via caveolae, however the structures and mechanisms for each pathogen are different. For example, *Escherichia coli (E.coli)* was one of the first bacteria demonstrated to invade the mast cell and macrophage via caveolae (Shin & Abraham, 2001). *E.coli*, a gram-negative bacteria and the most common cause of urinary tract infection, contains fimbriae or pili for binding to the host cell. The major virulence factor of *E.coli* is the FimH adhesin, a mannose-binding lectin located on the tips of fimbrial filament from the bacterial surface (Pizarro-Cerda & Cossart, 2006). The receptor of FimH adhesin on the mast cell has been identified as a glycosylphosphatidylinositol anchored protein or CD48, which is located in caveolae, therefore suggesting the involvement of caveolae in bacterial invasion (Pizarro-Cerda & Cossart, 2006). Disruption of caveolar system by using cholesterol-binding agents decreased the entry of the FimH expressing *E.coli* (Zaas et al., 2005). *Pseudomonas aeruginosa, Chlamydia trachomatis, Campilobacter jejuni* and Mycobacteria are some bacterial pathogens shown to utilize caveolae for invasion and survive within the host cells (Zaas et al., 2005). A number of pathogens invading the host cell by caveolar system are increasingly reported.

Conclusions

Since the discovery of caveolar system and caveolin in plasma membrane, it has been shown that these plasma microdomains play many important roles in physiological conditions as well as in human diseases. They represent various devices for compartmentalizing cellular membrane processes and signaling pathways. Caveolae contain numerous machinery molecules involved in vesicular trafficking, regulation of lipid and cholesterol content, receptors and signal transductions. In addition, caveolin proteins have been demonstrated to directly or indirectly interact with those molecules located in caveolae. The disruption of caveolae structure or the mutation of caveolin, especially at the scaffolding domain has been implicated in pathogenesis of many diseases, such as cancers, atherosclerosis, muscular dystrophy and bacterial infections. From what is already known, the caveolae and caveolins are one of potential therapeutic strategies to develop for clinical uses. However, many of the cellular biology of caveolae, caveolin and other molecules located within caveolar system need further studies. Research tools in cellular and molecular techniques have been established to answer questions still left in the caveolar system. For instance, the knockout mice or recombinant-antisense cDNA techniques are undergone development in many laboratories. Researches on the plasma membrane microdomains are now ongoing and more new data are generated everyday.

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