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Minireview

# Role of caveolin-1 and caveolae signaling in endotoxemia and sepsis ☆

Hong Feng [a], Wen Guo [b], Junqing Han [a], Xiang-An Li [c,*]

[a] Department of Tumor Research and Therapy Center, Provincial Hospital Affiliated to Shandong University, Jinan, Shandong 250021, China
[b] Taian Central Hospital, Taian, Shandong 271000, China
[c] Department of Pediatrics, University of Kentucky College of Medicine, Lexington, KY 40536, United States

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ABSTRACT

Caveolae, plasma membrane invaginations of 60–80 nm in diameter, are a subset of lipid rafts enriched in cholesterol and sphingolipids. Caveolae are expressed in various tissues and cell types, such as endothelial cells, macrophages, neutrophils and adipocytes. The functions of caveolae are diverse and include endocytosis, transcytosis, potocytosis, calcium signaling, and regulation of various signaling events. Although growing evidence has increased our understanding of caveolae function, the role of caveolae in sepsis is still a controversial issue. In this review, we present a number of studies addressing caveolae and sepsis and describe the signaling pathways involved, including the LPS-eNOS-TLR4-NFκB, MKK3/p38 MAPK, cPLA2/p38 MAPK, STAT3/NFκB and IL-1β-IL-1R1 pathways. Different studies using endotoxemia and bacteremia animal models have provided distinct conclusions about the function of caveolae, and we discuss these inconsistencies. Taken together, the current data suggest that the function of caveolae in sepsis, which involves a number of signaling pathways, is complex and warrants further studies.

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**Contents**



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* Corresponding author. Tel.: +1 859 257 5113; fax: +1 859 257 2120.
*E-mail address:* xli2@email.uky.edu (X.-A. Li).

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## Introduction

Caveolae, plasma membrane invaginations of 60–80 nm in diameter, were first identified in the 1950s by electron microscopy (Palade, 1953). Caveolae are a subset of lipid rafts that are enriched in cholesterol and sphingolipids. Caveolae are expressed in various tissues and cell types, such as smooth muscle, fibroblasts, endothelial cells, macrophages and adipocytes. The functions of caveolae are diverse and include endocytosis, transcytosis, potocytosis, calcium signaling, and regulation of various signaling events (Parton and Simons, 2007).

The major constituent of caveolae is the protein caveolin (Rothberg et al., 1992). There are three isoforms of caveolin, caveolin-1, 2, and 3. Caveolin-1 and 2 are expressed ubiquitously, whereas caveolin-3 is muscle-specific. Caveolin-1 is the most studied of these and the first member of the caveolin family to be identified. It is a 22-kDa tyrosine-phosphorylated protein and is known to be a structural component of caveolae and of transport vesicles derived from the trans-Golgi network (Igbavboa et al., 2009; Lin et al., 2009). Caveolin-1 is ubiquitously expressed, albeit at different levels in specific tissues. Disruption of the caveolin-1 gene leads to loss of caveolae (Drab et al., 2001), indicating an essential role of caveolin-1 in caveolae formation. As caveolin-1 is the defining and functional protein of caveolae, most studies have focused on it, especially those addressing the roles of caveolae in sepsis (Zemans and Downey, 2008).

## Function of caveolae and caveolin

Mice genetically deficient in caveolin-1 have been employed for studying the functions of caveolae and caveolin-1 (Drab et al., 2001). Caveolin-1-deficient mice generally appear healthy, but they are physically weak, and their lungs display severe abnormalities, with increased cell numbers and disorganized architecture. Subsequent studies have uncovered the functions of caveolin-1 in multiple biological processes, regulating cholesterol trafficking, signal transduction and tumorigenesis.

### *Cholesterol*

Cholesterol is required for the formation and maintenance of caveolae. Caveolin-1 can bind free cholesterol and has been implicated in the intracellular transport and regulation of cholesterol. A series of studies have demonstrated that caveolin-1 directly binds and traffics cholesterol through the cytoplasm to the plasma membrane in a lipoprotein chaperone complex (Igbavboa et al., 2009; Lin et al., 2009).The chaperone complex consists of caveolin-1, cyclophilin A, cyclophilin 40 and HSP56. A caveolin-1 lipoprotein chaperone complex was also shown to facilitate the uptake of caveolae cholesterol (Lin et al., 2009). Caveolin-1 facilitates this uptake by forming a lipoprotein complex consisting of caveolin-1, cyclophilin A, cyclophilin 40 and annexin II. Thus, caveolin-1 appears to shuttle between the plasma membrane and the Golgi by a multi-step process. Evidence also suggests that caveolin-1 is involved in the transport of newly synthesized cholesterol from the ER to the plasma membrane. Fu et al. (2010) reported that cholesterol increases the adhesion of monocytes to the endothelium by moving adhesion molecules out of caveolae, suggesting that caveolin-1 may also affect inflammatory processes through its interaction with cholesterol.

### *Signal transduction*

Previous reports have presented caveolae as lipid-based signaling platforms that both compartmentalize and concentrate signaling molecules. However, recent studies emphasize the importance of caveolins, including caveolin-1, as negative regulators of diverse cellular signaling pathways (Dessy et al., 2010). Specific motifs within the caveolin proteins serve to recruit lipids and proteins to caveolae, thus facilitating intracellular trafficking of the cellular machinery and regulation of signaling pathways. Sequestered within caveolae, through interaction with caveolin-1, are many G protein receptors, Gα subunits, tyrosine kinases and receptor tyrosine kinases, GTPases, components of the MAPK pathway, and others (Cao et al., 2002; Vargas et al., 2002; Vihanto et al., 2006). In many of these interactions, caveolin-1 appears to dampen signaling pathways by inhibiting the associated proteins, including c-Src, H-Ras, mitogen-activated protein (MAP) kinases (Engelman et al., 1998) and eNOS (Brouet et al., 2001; Garrean et al., 2006; Ju et al., 1997; Mirza et al., 2010; Sessa, 2005; Shin et al., 1996; Wang and Abdel-Rahman, 2005). Some of these proteins are important participants in sepsis, implying a role for caveolae in this process.

## The role of caveolae and caveolin in sepsis

### *Distribution of caveolae and caveolin in immune cells*

Although caveolae and caveolin have been implicated in immune response processes, their presence in immune cells is still a contentious issue (Harris et al., 2002a). Most research suggests that they are commonly found in myeloid cells. Caveolae or caveolin has been identified in murine macrophages and mast cells, in human dendritic cells and in bovine monocytes, macrophages and dendritic cells (Harris et al., 2002b; Shin et al., 2000; Wang et al., 2006). Caveolin has also been reported in human neutrophils (Hu et al., 2008), the professional phagocytic immune cells, suggesting that caveolae and caveolin play an important role in specific immune cell functions. Most recent evidence suggests that caveolae and caveolin are present in all types of immune cells, including lymphocytes, although different results have been presented (Fra et al., 1995; Medina et al., 2006b; Vallejo and Hardin, 2005). The presence of caveolae or caveolin in human and murine lymphocytes might depend on the cell type studied, and their expression or distribution might also be dependent on the activation and/or maturation state of the cell. The universal distribution of caveolae and caveolin-1 in immune cells suggests they might be involved in sepsis.

### *The role of caveolae in pathogen internalization*

Caveolae have long been suggested to play a role in innate immunity, and pathogen–caveolae interactions have been reported. In many cases, particularly for bacterial pathogens and their exotoxins, such interactions might have evolved to facilitate the entry of the pathogen into host cells, avoiding routes that would lead to pathogen destruction.

Under serum-free conditions, *Escherichia coli* that binds to macrophages through FimH (a mannose-binding fimbrial lectin that promotes bacterial adherence and colonization of mucosal surfaces) can survive inside the macrophage (Baorto et al., 1997). The receptor for FimH is GPI-linked CD48, which is concentrated in the caveolae of macrophages and mast cells. Internalization of FimH-expressing *E. coli* is inhibited by the caveolae-disrupting agents filipin, nystatin and methyl-β-cyclodextrin (Baorto et al., 1997; Shin et al., 2000). Under nonopsonic conditions, *Chlamydia trachomatis* has been shown to enter HEp-2 and HeLa 299 endothelial cells, as well as J-774A.1 mouse macrophage/monocyte cells, through caveolin-positive membrane domains enriched in glycosphingolipids and cholesterol; this entry can be inhibited with nystatin or filipin (Norkin et al., 2001). Caveolae have also been implicated in the cellular transport of viruses, including simian virus 40, respiratory syncytial virus and human immunodeficiency virus. The presence of caveolae thus facilitates the survival of pathogens inside the host cells, implicating caveolae as important regulators of infectious diseases.

### *The role of caveolae signaling in the response to LPS-induced endotoxemia*

Using different cell lines, Lei and Morrison (2000) observed different changes in caveolin-1 expression in response to various LPS concentrations. Similarly, Tiruppathi et al. (2008) reported that LPS challenge of

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