Available online at www.sciencedirect.com
ScienceDirect
Cancer Letters 268 (2008) 187–201
CANCER Letters
www.elsevier.com/locate/canlet

Mini-review

# Caveats of caveolin-1 in cancer progression

Elke Burgermeister [a,*], Mordechai Liscovitch [b], Christoph Röcken [c], Roland M. Schmid [a], Matthias P.A. Ebert [a]

[a] *Department of Medicine II, Klinikum rechts der Isar, Technical University of München, Ismaningerstrasse 22, D-81675 München, Germany*
[b] *Department of Biological Regulation, The Weizmann Institute of Science, Rehovot, Israel*
[c] *Department of Pathology, Charite, Berlin, Germany*

Received 9 January 2008; received in revised form 25 March 2008; accepted 25 March 2008

**Abstract**

Caveolin-1, an essential scaffold protein of caveolae and cellular transport processes, lately gained recognition as a stage- and tissue-specific tumor modulator *in vivo*. Patient studies and rodent models corroborated its janus-faced role as a tumor suppressor in non-neoplastic tissue, its down-regulation (loss of function) upon transformation and its re-expression (regain of function) in advanced-stage metastatic and multidrug resistant tumors. This review is focussed on the role of caveolin-1 in metastasis and angiogenesis and its clinical implications as a prognostic marker in cancer progression.


*Keywords:* Cancer progression; Caveolin; Metastasis; Angiogenesis; Prognosis

## 1. Introduction: caveolin-1, a versatile scaffold protein

Caveolin-1, a ~21- to 24-kDa scaffold protein, is the essential constituent of caveolae, flask-shaped (50–100 nm) invaginations that can occupy up to 20% of the plasma membrane (for extensive review [1–3]). Caveolin-1 (caveolin-3 in skeletal muscle cells) belongs to a highly conserved gene family and is co-expressed with caveolin-2 in cells and tissues of mesenchymal, endo/epithelial, neuronal/glial origin. The caveolin-1 gene is composed of three exons and alternatively translated into the endoplasmatic reticulum (ER) as a full-length 178 amino acids (aa) α-isoform and a β-isoform lacking the first 32 aa (Fig. 1). Caveolins are membrane proteins with a unique hairpin conformation where both N- and C-termini are exposed to the cytoplasm. A central membrane spanning domain (TMD), C- and N-terminal membrane attachment domains (MAD) and three palmitoyl groups at the C-terminus enable its insertion into the inner leaflet

*Abbreviations:* Cav-1, caveolin-1; KO, knock-out; NOS, nitric oxide synthase; NR, nuclear receptor; MDR, multidrug resistance; GI, gastrointestinal tract; TJ, tight junction; ZA, adherens junction; ECM, extracellular matrix; VSMC, vascular smooth muscle cells; EC, endothelial cells; MMP, matrix metalloproteases; PDAC, pancreatic ductal adenocarcinoma; GC, gastric adenocarcinoma; CSD, Cav-1 scaffolding domain; MAD, membrane attachment domain; TMD, transmembrane domain.

* Corresponding author. Tel.: +49 89 4140 6792; fax: +49 89 4140 6796.
*E-mail address:* elke.burgermeister@lrz.tum.de (E. Burgermeister).

0304-3835/$ - see front matter © 2008 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.canlet.2008.03.055

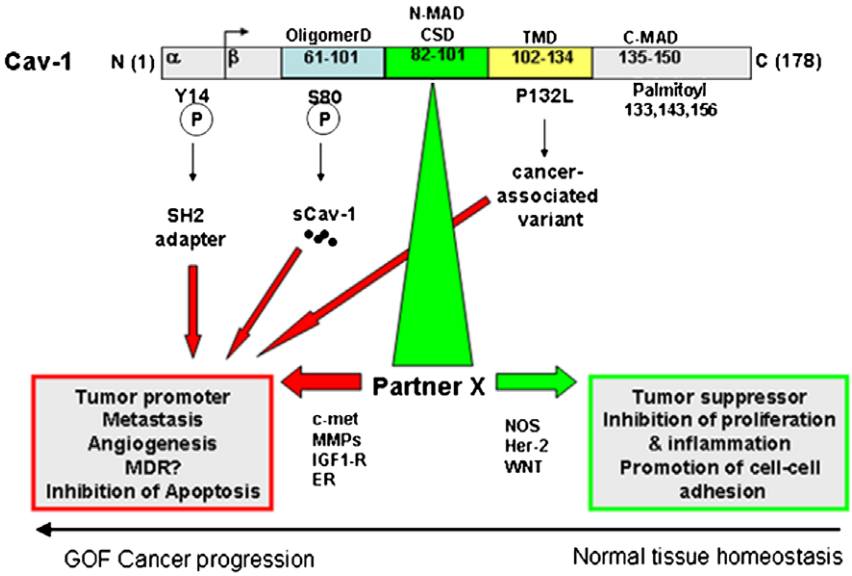


Fig. 1. Model of the structure and function of caveolin-1 in cancer progression. In non-neoplastic tissue, the scaffolding domain (CSD) interacts with different protein partners X that maintain normal tissue homeostasis and metabolism (e.g. membrane cholesterol). During tumor initiation, beneficial tumor suppressive partners are lost and substituted by tumor-promoting proteins to facilitate tumor progression. Post-translational modifications and altered subcellular compartmentalization of caveolin-1 further facilitate a switch from tumor suppressor to tumor promoter functions.

of the membrane. Caveolin-1 binds to cholesterol and sphingolipids within "lipid rafts" which are considered as specialized "detergent-insoluble cholesterol- and glycolipid-rich" (DIG) membrane microdomains (further reading in [4]). Upon exit from the ER/Golgi apparatus, caveolin-1 monomers, by means of their oligomerization domain (aa 61–101), assemble into high-molecular weight homo- and hetero-oligomers (with caveolin-2) to form the striated caveolar coat structure.

Caveolae mediate cellular transport processes such as cholesterol efflux, clathrin-independent endocytosis (a commonly exploited entry pathway of pathogens into host cells), lipid and protein sorting [1]. Caveolin-1 is a versatile protein which is also present in (i) "caveosomes", dynamic juxtamembranal transport vesicles that recycle between endosomal/lysosomal and Golgi compartments and (ii) as exocytotic/secretory or (iii) cytoplasmic/lipid-droplet associated form, that are both complexed with lipoprotein particles to facilitate its solubilisation. Nuclear caveolin-1 has been identified in chromatin-immunoprecipitations [5] which, however, awaits further validation. The multiple manifestations of caveolin-1 are indicative of topology- and compartment-specific cellular actions.

Caveolin-1 exerts its intrinsic function as a scaffold protein by interaction with partner proteins via its 'scaffolding' domain (CSD) (aa 82–101) that binds short peptide motifs rich in aromatic residues such as $\omega x_4 \omega x_2 \omega$ (omega = aromatic acid, x = any amino acid) (recently reviewed in [6]). Caveolin-1 thereby organizes protein and lipid molecules (receptors) at the plasma membrane into a "launching platform" for downstream signalling cascades, thereby representing a first-line checkpoint for the regulation of cell signalling [2,3]. Caveolin-1 controls signalling components by two ways, by (i) direct protein interaction (e.g. via its CSD) and as a result modulation of activity and (ii) regulation of internalization and thereby duration of the signal. Many receptors including those for growth factors (e.g. the Her2/*neu*/ErbB2/ras/raf/ERK cascade) and pro-inflammatory cytokines, cytosolic tyrosine kinases (*src*), nitric oxide synthases (NOS), G-proteins, etc. are inhibited through interaction with the caveolin-1 scaffolding domain, e.g. to restrict proliferation, vasodilation and inflammation; while others such as the insulin receptor or cell–cell (cadherins) and cell–matrix (integrins) adhesion molecules are kept in an active state to support tissue homeostasis, endothelial barrier functions, cell survival, migration and differentiation,