Role of Caveolin 1 in Neoplastic Skin Diseases: A Great Controversy

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ABSTRACT.

The caveolar membrane is primarily composed of cytoplasmic proteins known as caveolins, identified in the nineties. TGF-β, matrix metalloproteinases, heat shock proteins, toll-like receptors, and other signaling molecules and receptors interact physically with caveolin-1, which is highly expressed in dermal and subdermal cells. Caveolin-1 is likely to play an important role in controlling cell proliferation and inflammation when they occur together. Caveolin-1 expression is discussed concerning several hyperproliferative, inflammatory, and neoplastic skin diseases.

Keywords: Caveolin 1; squamous cell carcinoma; basal cell carcinoma; melanoma

1. INTRODUCTION

The caveolin family of membrane-bound scaffolding proteins performs a critical function in signal transduction [1]. There are three isoforms of caveolin that have indeed been identified in mammalian species: caveolin-1, caveolin-2, and caveolin-3. Caveolin-1 has already been demonstrated to influence the activities of various transduction pathways, primarily through inhibitory impacts on kinase activities related to cell proliferation [2]. Caveolin-1 may perform an important role in the pathogenesis of nonmelanoma skin cancers [NMSCs]. Caveolin-1 may be beneficial as a prognostic biomarker for people at risk of disease progression [2]. Additionally, it is found in malignant melanoma. We shall explore the role of caveolin 1 in neoplastic skin diseases in this article.

BCC, as well as SCC, are NMSC. BCC seems to be the most frequently occurring type of nonmelanoma skin cancer. BCC is the least aggressive type of nonmelanoma skin cancer. Furthermore, despite its capacity for local invasion, tissue damage, relapse, and a restricted capacity for metastasis, BCC has a minimal degree of malignancy [3]. SCC, on the contrary, is defined by an abnormal proliferation of invasive squamous cells that have the potential to spread. Additionally, SCC demonstrates a high risk for relapse [4]. While actinic keratosis [AK] is the most often occurring in situ skin carcinoma [5].

2. Structure of caveolin

CAV-1, CAV2, and CAV3 make up the caveolin protein family. In striated muscle and cardiac muscle cells, CAV-1 and CAV-2 are expressed in all tissues. Muscle-specific caveolin Cav-3, commonly referred to as M-caveolin, is a kind of caveolin [6] Cav-1 is found in all tissues. However, its levels vary depending on the type. When CAV-1 is present inside cells, it is mainly
located on the plasma membrane and in the mitochondria, nucleus, Golgi complex, and endoplasmic reticulum membranes. The lung is the most predominant organ in which caveolin 1 is expressed. As opposed to type II cells [ATII], alveolar epithelial type I cells [ATI] express CAV-1 nearly exclusively in the lung epithelium [7].

The N-terminal domain, scaffolding domain, intramembrane domain, and C-terminal domain are all part of Cav-1’s four major structural domains. It has a hairpin-like structure and has a molecular mass of 20.5 kDa. CAV-1’s N- and C-terminal tails, which face the cytoplasm, are separated by a hydrophobic intramembrane loop structure [8]. Cav-1 has two well-characterized isoforms, cav-1α and cav-1β. However, recent articles show that these isoforms perform various functions in the development of the fetal lung and blood vessels [9].

3. The function of cav-1

Caveolin 1 plays a critical role in lipid transporting [10], membrane trafficking [11], cell signaling [12], cell migration [13], and cell proliferation [14], which are all necessary for optimal skin functionality. Additionally, Cav-1 plays a role in pathophysiological skin diseases associated with Cav-1 dysfunction, including skin cancer [15], scleroderma [16], psoriasis [17], alopecia [18], and skin alterations associated with aging [19], and also chronic wounds that do not heal [20].

4. Role of caveolin 1 in neoplastic diseases

Caveolin either promotes or suppresses tumor growth based on the type and stage of the tumor. In terms of tumor promotion, it has already been observed that increased CAV-1 expression promotes tumorigenesis by suppressing apoptosis, allowing anchorage-independent growth, treatment resistance, and metastasis [21]. For example, CAV-1 expression was observed to associate favorably with differentiation status, enhanced portal vein invasion, intrahepatic metastases, and to predict survival rates in patients suffering from liver malignancies. Furthermore, in vitro, mechanistic studies revealed that overexpression of CAV-1 increased recognized migration and invasion mediators, particularly matrix metalloproteinases 2 and 9 and vascular epidermal growth factor [22].

In colorectal, breast, lung, and liver malignancies, caveolin serves as a tumor suppressor. Also, decreased stromal CAV-1 expression is correlated with reduced survival rates in breast cancer. In lung cancer cell lines, CAV-1 deregulation stimulates proliferation, whereas overexpression triggers apoptosis. Additionally, reducing the expression of Cav-1 prevents senescence, simultaneously encouraging lung tumors’ growth and increasing death rates [23]. Carcinogenesis is influenced by epigenetic control of CAV-1-associated proteins. For example, hypermethylation of the Polymerase I and transcript release factor (PTRF)/cavin1 promoter inhibits the creation of caveolae and the development of Ewing sarcoma. Reintroducing PTRF/cavin1 and CAV-1 enhances the number of caveolae, induces apoptosis, and shrinks tumors [24].

The signaling pathways implicated in CAV-1-associated tumor suppression have been studied extensively. CAV-1 has also been shown to affect cell proliferation and apoptosis of human lung cancer. Through contacts at the plasma membrane, particularly the scaffolding domain, CAV-1 blocks cadherin-11/Stat3/Rac1 signaling in these cells. Furthermore, CAV-1 promotes
E-cadherin and p120-Catenin localization to the plasma membrane and establishes adherent junctions in ovarian cancer cell lines, limiting tumor cell spreading via metastases [26].

5. Role of cav-1 in skin cancer (table 1)

1-Role of cav-1 in nonmelanoma skin cancer

ROLE OF CAV-1 IN BASAL CELL CARCINOMA

In BCCs, caveolin-1 expression was considerably decreased. Caveolin-1 expression is significantly decreased in aggressive forms of BCC [which include micronodular, infiltrative, as well, as metatypical BCC], particularly in comparison to nonaggressive forms [such as nodular as well as superficial BCC], implying that caveolin-1 may be effective in predicting the biological behavior of BCC and identifying patients at increased risk of poor prognosis [2].

Table 1 Caveolin 1 expression in neoplastic skin diseases

<table>
<thead>
<tr>
<th>Neoplastic skin diseases</th>
<th>Level of caveolin 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actinic keratosis [premalignant]</td>
<td>Increased [tumor promtor]</td>
</tr>
<tr>
<td>Yun et al., 2019 [27]</td>
<td></td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>Decreased [tumor suppressor]</td>
</tr>
<tr>
<td>Gheida et al., 2018 [2]</td>
<td></td>
</tr>
<tr>
<td>Jaafari-Ashkavandi and Aslani., 2017 [28]</td>
<td>Increased [tumor promtor]</td>
</tr>
<tr>
<td>Basal cell carcinoma</td>
<td></td>
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<tr>
<td>Gheida et al., 2018 [5]</td>
<td>Increased [tumor promtor]</td>
</tr>
<tr>
<td>Melanoma</td>
<td>Decreased [tumor suppressor]</td>
</tr>
<tr>
<td>Tas et al., 2016 [30]</td>
<td>Increased [tumor promtor]</td>
</tr>
<tr>
<td>Nakashima et al., 2007 [31]</td>
<td>Decreased [tumor suppressor]</td>
</tr>
<tr>
<td>Sarcoma</td>
<td></td>
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<tr>
<td>Sáinz-Jaspeado et al., [2011][33]</td>
<td>Decreased [tumor suppressor]</td>
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Role of cav-1 in actinic keratosis

Precancerous lesions such as actinic keratoses and keratoacanthomas form before a human skin tumor may develop. Compared to normal skin, the expression of caveolin 1 in actinic keratoses is significantly high, and it is associated with the extent of malignancy [27].

ROLE OF CAV-1 IN SQUAMOUS CELL CARCINOMA

The role of cav-1 in squamous cell carcinoma is controversial. It may act as a tumor suppressor or promoter. SCC of the mouth and head and neck SCC show overexpression of Cav-1 [28]. Cav-1 expression was considerably reduced [29]. When comparing types level of cav-1 was decreased in poorly differentiated types than well-differentiated types. This finding shows that caveolin-1 downregulation is involved in tumor development and tumor progression, indicating that caveolin-1 can be used as a prognostic biomarker in the future [2].

There is a correlation between Cav-1 overexpression and reduced in vitro cell proliferation and in vivo tumor incidence, volume, and weight in murine models of skin SCC [28]. When mice are deficient in Cav-1, they develop more aggressive cancers and have higher invasion rates and spontaneous lymph node metastasis. This suggests that Cav-1 may behave as a controller of cancer invasion and metastasis in cutaneous SCCs by regulating MAPK pathway hyperactivity, which is probably the case when mice are deficient in the protein [28].

2-Role of cav-1 in melanoma

In melanoma, the role of caveolin 1 as a tumor suppressor or tumor promoter is much more controversial. Several investigations have indicated elevated Cav-1 concentrations in melanoma patients, with baseline serum Cav-1 levels significantly greater than those in the control group [30]. An additional study discovered that upregulation of Cav-1 in human melanoma cell lines inhibited cell proliferation and migration. In contrast, further studies confirm Cav-1’s tumor-suppressive involvement in melanoma by detecting its regulation of metastasis [31]. For instance, whenever the link between Cav-1 levels and survival in primary malignant melanoma and melanoma lymph node metastases was studied, it was discovered that loss of Cav-1 expression in melanoma cells anticipates lower survival in primary malignant melanoma.

Cav-1 levels in the stroma were found to be strong predictors of the clinical outcome once the tumor started to metastasize, but not in melanoma cells. Deficiency of stromal Cav-1 resulted in melanoma invasion and metastases, revealing aggressive behavior. There has been no prior evidence that Cav-1 acts as a metastasis suppressor in the stromal compartment of malignant melanomas. This finding suggests that Cav-1 could be valuable as a potential biomarker of melanomas and that stromal-targeted therapy effectively suppresses tumor growth [32].

3-Role of cav-1 in sarcoma

CAV-1 is commonly present in adipocytes, smooth muscle cells, endothelial cells. Immunohistochemical techniques found that CAV-1 expression was widespread in fibroblasts, smooth muscle cells, adipocytes, and endothelial cells. The staining pattern was fine granular membranous and diffused in the cytoplasm. CAV-1 concentrations in benign mesenchymal tumors were comparable to those in normal mesenchymal cells in all of the patients’ tumors except for the fibromatosis. CAV-1 expression was absent or considerably reduced in
fibrosarcomas, leiomyosarcomas, angiosarcomas, malignant fibrous histiocytomas, and synovial sarcomas. Thus, CAV-1 has been identified as a potential tumor suppressor gene in sarcoma [33].

6. Prospective future

Due to the variety of Cav-1 expression in tumor types, therapeutics targeting Cav-1 must consider the distinct key roles of this protein inside each kind of tumor cell. It was discovered that the Cav-1 promoter might be used in an innovative gene therapy strategy to directly targets malignant prostate cells while causing minimal damages to the neighboring healthy cells.

5-aza-2'-deoxycytidine, a DNA hypomethylating drug, restores CAV-1 expression in various forms of malignancies. CAV-1 expression is upregulated in colon cancer cells treated with histone deacetylase inhibitors like trichostatin A, which inhibits cell proliferation [34].

7. CONCLUSION

Caveolin 1 has either tumor-promoting or tumor-suppressive properties depending on the type of tumor. As a prognostic indicator of disease severity, caveolin 1 may be valuable. Caveolin 1 can indeed be utilized as anticancer therapy.

Funding: No funding was received for this study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

Conflicts of Interest: The authors declare no conflict of interest.

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