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# Is caveolin-1 a biomarker for resistance to radiotherapy?

**Y.B. Cihan, B. Tekin**

*Department of Radiation Oncology, Kayseri Education and Research Hospital, Kayseri, Turkey*

Η caveolin-1 συνιστά βιοδείκτη για αντίσταση στη θεραπεία με ακτινοβολία;

*Περίληψη στο τέλος του άρθρου*

**Key words:** Biomarker, Caveolin-1, Radiotherapy

In recent years, studies on the interaction of extracellular matrix, membrane and intracellular proteins with a specialized lipid raft and caveola structures have been intensified.

Caveola is the indentation of membrane receptors, for substances which are far from being able to come together under normal conditions to induce their interaction and to activate themselves and each other. Caveola plays an important role in the transmission of endocytosis, tumorigenesis, cholesterol regulation and signal transduction. The main components of Caveola are caveolin and the caveolin (CAV) family proteins. In Caveola, various cells, including adipocytes, endothelial cells and fibroblasts, and the plasma membranes of mesenchymal cells are located in a specialized lipid rafts, acting as the membrane regulatory center. The occurrence and continuity of Caveola is mediated by caveolin (CAV) proteins. The CAV protein family has three sub-members, CAV-1, CAV-2 and CAV-3. Since CAV-1 is responsible for the structural order, it is the most important structural protein of Caveola and its expression is widely observed. CAV-1 is generally expressed in large amounts in smooth muscle cells, endothelial cells, adipocytes and fibroblasts.[1–5]

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CAV-1 is the most extensively monitored member of this family of proteins. It plays a role in many cellular events such as cellular mutations, proliferation and apoptosis. The importance of CAV-1 has been emphasized by studies on its effect in tumors and metastasis. While CAV-1 expression is low in the first stage of tumor formation, it increases in advanced stage cancer and in the metastatic process. For this reason, it appears that CAV-1 acts as a tumor suppressor in the early stages of tumor formation process and as an oncogene by stimulating migration and metastasis in the advanced stages. CAV-1, with reduced expression shows a negative correlation with the development of breast cancer, colon cancer, lung cancer, and ovarian cancer. A positive correlation has been demonstrated between CAV-1 expression upregulation and breast cancer, non-small lung cell carcinoma (NSCLC), bladder cancer, prostate cancer, esophageal cancer and pancreatic cancer metastasis, and upregulation is associated with poor prognosis.[1–3]

In recent years, it has been proposed that CAV-1 can be used as a biomarker for radiotherapy in the treatment of cancer. One of the main challenges for the effective clinical outcome of radiotherapy in cancer patients is the development of radioresistance during radiation therapy, which makes radiation therapy a less effective modality.[3–9] In an *in vitro* study conducted by Zou the attenuation of CAV-1 knockdown of human basal-like triple-negative breast cancer cells increased radiosensitivity.[5] In their review, Mahmood and colleagues reported that CAV-1 could be a new prognostic biomarker for monitoring tumor radiotherapy in prostate, pancreatic and lung cancer.[4]

Panic and colleagues, in their study on the response of radiation in human PC3 xenografts, reported that the loss of stromal CAV-1 expression in advanced tumor stages may cause radioresistance.[6] Recent research reports on cell cultures have demonstrated the role of CAV-1 in tumor radiotherapy and poor treatment outcomes.[4–7] There are a limited number of Phase 2 and 3 studies showing that CAV-1 causes radioresistance in cancer. Zou and colleagues evaluated the role of CAV-1 expression in predicting the

survival and responsiveness to radiotherapy in 69 patients with NSCLC brain metastasis. Among factors investigated, only CAV-1 expression was associated with poor prognosis and increased risk of death in brain metastasis (log-rank test, p=0.015). Among the patients treated with radiotherapy, there was an increased risk of death in the group with CAV1-positive brain metastasis (p=0.004). In conclusion, they emphasized the predictive role of CAV-1 expression for shorter survival and resistance to radiotherapy.[5]

Rödel and colleagues investigated the prognostic value of CAV-1 in patients with rectal cancer who underwent preoperative chemoradiation therapy. CAV-1 mRNA and protein expression were assessed by Affymetrix microarray analysis (n=20) and immunohistochemistry (n=44) in biopsy samples. For patients with low CAV-1 expression tumors, the local 5-year control rates were significantly better than carcinoma cells expressing high cyanobom-1 (p=0.05; 92%, 95% confidence interval [95% CI]: 82%, 102%, and 72%, 95% CI: 49–84%), they concluded that CAV-1 may be a new prognostic marker for local control and survival in patients with rectal cancer.[9]

As a result, it can be concluded that CAV-1 plays an important role in modulating tumor host interactions by supporting tumor growth, metastasis, radiation treatment resistance and cell survival. It is suggested that in cancer patients undergoing radiation therapy CAV-1 may be a new biomarker for predicting favorable clinical outcomes. This biomarker may also be important for the early diagnosis of malignant diseases, monitoring the prognosis in patients with cancer, and provision of appropriate treatment.

## ΠΕΡΙΛΗΨΗ

### Η caveolin-1 συνιστά βιοδείκτη για αντίσταση στη θεραπεία με ακτινοβολία;

Y.B. CIHAN, B. TEKIN

*Department of Radiation Oncology, Kayseri Education and Research Hospital, Kayseri, Τουρκία*

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Η caveolin-1 διαδραματίζει σημαντικό ρόλο στη διαμόρφωση των αλληλεπιδράσεων του ξενιστή του όγκου, υποστηρίζοντας την ανάπτυξη του όγκου, τις μεταστάσεις, την αντίσταση στη θεραπεία με ακτινοβολία και την επιβίωση των κυττάρων. Η CAV-1 μπορεί να είναι ένας νέος βιοδείκτης σε ασθενείς με καρκίνο που υποβάλλονται σε ακτινοθεραπεία προκειμένου να βελτιωθεί η κλινική πορεία. Η αναγνώρισή του ενδέχεται είναι σημαντική για την έγκαιρη διάγνωση κακοήθων νόσων, για την παρακολούθηση της πρόγνωσης σε ασθενείς και τη χορήγηση της κατάλληλης θεραπείας.

**Λέξεις ευρετηρίου:** Ακτινοθεραπεία, Βιοδείκτης, Caveolin-1

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*Corresponding author:*

Y.B. Cihan, Department of Radiation Oncology, Kayseri Education and Research Hospital, 38010 Kayseri, Turkey
e-mail: cihany@erciyes.edu.tr