



# Syndecan-1 as a therapeutic target in squamous cell carcinoma: Current insights and future directions

Rita Files<sup>1\*</sup> , Cláudia Cardoso<sup>1</sup>, Justina Prada<sup>1,2</sup> , Filipe Silva<sup>1,2</sup> , Isabel Pires<sup>1,2</sup> 

<sup>1</sup>Department of Veterinary Sciences, University of Trás-os-Montes and Alto Douro, Vila Real, Portugal.

<sup>2</sup>Animal and Veterinary Research Centre (CECAV), Associate Laboratory for Animal and Veterinary Sciences (AL4AnimalS), University of Trás-os-Montes and Alto Douro, Vila Real, Portugal.

## ARTICLE HISTORY

Received on: 30/07/2024  
Accepted on: 06/10/2024  
Available Online: 05/01/2025

### Key words:

Syndecan-1, therapeutic target, cancer, cutaneous squamous cells carcinoma, biomarker.

## ABSTRACT

Squamous cell carcinoma (SCC) is a type of epithelial cancer that originates in the squamous epithelium and can develop in any area of the body covered by this tissue. Cutaneous SCC is characterized by a locally aggressive tumor, highlighting the importance of identifying new therapeutic targets to combat this disease effectively. Syndecan-1, a molecule often deregulated in cutaneous SCC, is a type 1 transmembrane proteoglycan primarily expressed in epithelial and plasma cells. The ectodomain of Syndecan-1 is frequently shed, rendering the molecule soluble and capable of interacting with various other molecules. This review aims to comprehensively analyze Syndecan-1 expression in cutaneous squamous cell carcinoma (CSCC), elucidate its role in tumorigenesis, and assess promising therapeutic strategies that target Syndecan-1 and its associated pathways. Therapeutic approaches often focus on molecules that facilitate the shedding of the Syndecan-1 ectodomain, such as matrix metalloproteinases (MMPs) and heparanase. Inhibition of heparanase and MMPs has shown potential in preventing the degradation of Syndecan-1 and reducing tumor invasiveness. Additional strategies include using synthetic proteoglycans, peptide mimetics such as syntenin, and overexpression of the C-terminal fragment of Syndecan-1 to suppress tumor growth and migration. Moreover, targeting microRNAs that regulate Syndecan-1 expression presents another promising therapeutic tool. These therapies are designed to modulate the function of Syndecan-1, potentially affecting the progression of CSCC and improving clinical outcomes.

## INTRODUCTION

Cancer is a complex group of diseases characterized by abnormal cellular proliferation that progress through various stages, transforming normal cells into neoplastic cells. The fundamental traits necessary for tumor development include sustained proliferative signaling, evasion of growth suppressors, acquisition of replicative immortality, potential for invasion and metastasis, induction of angiogenesis, and resistance to cell death. These traits are commonly referred to as the “hallmarks” of cancer. They are associated with specific deregulated genes and molecular

mechanisms. As our understanding of the biological processes underlying cancer development and progression deepens, new cancer biomarkers are being identified, providing insights into the disease’s evolution. For instance, changes in DNA methylation, genetic mutations, alterations in microRNA levels, and the presence of circulating proteins or nucleic acids in the blood or tissue can be significant indicators of cancer onset and progression [1,2].

The detection and analysis of neoplastic biomolecular alterations enable early identification of cancer, monitoring its progression, and predicting treatment responses, thereby facilitating more personalized and effective patient care. Consequently, exploring new biomarkers that offer detailed insights is essential for advancing the fight against cancer [1,2].

Squamous cell carcinoma (SCC) is a common type of skin cancer that occurs in both humans and dogs. While this carcinoma often presents benign clinical behavior, it can also

### \*Corresponding Author

Rita Files, Department of Veterinary Sciences, University of Trás-os-Montes and Alto Douro, Vila Real, Portugal.  
E-mail: [ritafiles2000@gmail.com](mailto:ritafiles2000@gmail.com)

exhibit local invasion and metastatic potential characteristics. In most cases, the classical treatment involves the surgical removal of the tumor. However, over time, a growing number of mutations, biomolecules, and pathways associated with SCC have been identified, driving the development of new and more effective therapies [3,4].

Syndecan-1, a heparan sulfate proteoglycan, maintains normal cell morphology. Its interactions with various extracellular and intracellular proteins and its mediation of cell signaling in response to environmental stimuli make it a significant factor in cancer biology. Syndecan-1 is involved in several key processes essential for tumorigenesis, including cell growth and migration, apoptosis, angiogenesis, invasion, and metastasis. In cases of skin cancer, including SCC, the compromised function of Syndecan-1 may significantly contribute to tumor progression [5–7].

This review will discuss the expression Syndecan-1 in SCC and the potential for future therapies based on modulating this marker's expression.

## METHODS

A comprehensive literature search was conducted using specific keywords and multiple databases to investigate the role of Syndecan in SCC and explore potential therapeutic strategies. The primary keywords used in this search included “Syndecan,” “SCC,” “Syndecan-1,” “Syndecan-4,” “Syndecan inhibition,” “Syndecan gene therapy,” “Syndecan-targeted therapy,” “SCC treatment,” “cancer cell proliferation and migration,” and “extracellular matrix interactions in SCC.” These keywords were strategically combined using Boolean operators (AND, OR) to refine the search and target specific aspects of the research topic. For instance, combinations such as “Syndecan AND SCC,” “Syndecan-1 OR Syndecan-4 AND SCC,” “Syndecan inhibition AND SCC treatment,” and “extracellular matrix AND Syndecan AND SCC” were employed to ensure comprehensive coverage of relevant studies.

The literature search was conducted across multiple databases, including PubMed, Scopus, Web of Science, and Google Scholar, to ensure an extensive collection of relevant studies. This multi-database approach utilized both broad and specific search queries to capture a wide range of articles related to the role of Syndecan in SCC and its therapeutic implications.

After the search, the selected articles were thoroughly reviewed, and relevant data were extracted. The extracted data were then synthesized to comprehensively understand Syndecan's multifaceted role in SCC and identify promising therapeutic strategies.

## CUTANEOUS SQUAMOUS CELL CARCINOMA (CSCC)

SCC is one of the most common malignant neoplasms, frequently occurring in the head and neck, cervix, esophagus, lungs (non-small cell tumors), and skin. This malignancy arises from the uncontrolled growth of epithelial cells and typically occurs in organs lined with squamous epithelium. Studies have shown that, regardless of the tissue of origin, patients with SCC exhibit common molecular characteristics, such as those associated with exposure to ultraviolet (UV) radiation. SCC has a significant tendency to metastasize to nearby lymph nodes and

distant organs, posing substantial challenges for both treatment and management of the disease [3].

CSCC, a type of keratinocyte carcinoma found in the epidermis or associated structures, is the most common form of non-melanoma skin cancer in both humans and dogs [4].

## Risks associated with the development of CSCC

Several risk factors are associated with CSCC, which can be environmental, genetic, or epigenetic. UV radiation is one of the primary contributors to this type of cancer [8]. Other risk factors include male gender, advanced age, fair skin, immunosuppression, chronic skin ulcers, HPV infection, smoking, certain medical conditions (such as chronic lymphocytic leukemia and non-Hodgkin's lymphoma), use of BRAF inhibitors, chronic skin inflammation, and genetic skin disorders like recessive dystrophic epidermolysis bullosa [9,10]. The complex molecular mechanisms associated with CSCC and its high mutational burden can lead to various clinical manifestations, including Bowen's disease, erythroplasia of Queyrat, and Bowenoid papulosis [9,11].

## Carcinogenesis and molecular changes in CSCC

Understanding the progression of CSCC requires identifying the genes involved and investigating new therapeutic strategies. CSCC is characterized by a high mutational load, often resulting from exposure to UV radiation, as discussed earlier [12]. Endogenous factors, including errors in DNA repair, genome editing, mitotic errors, and reactive oxygen species, can cause mutations. For CSCC to develop, mutations must occur in long-lived cells within the epidermal compartment, particularly in the basal layer [12,13].

One of the earliest genetic alterations in CSCC is the *TP53* tumor suppressor gene mutation, frequently induced by UV radiation [7]. Mutations in other genes, such as *p63* and *p73*, are also common. Additional genes that are often deregulated include the histone acetyltransferase *p300* (*EP300*), Polybromo-1 (*PBR1*), ubiquitin-specific peptidase 28 (*USP28*), and the conserved ubiquitinated helix-loop-helix kinase (*CHUK*). Mutations in *NOTCH1* and *NOTCH2*, which result in truncated Notch receptors and impaired signaling, are prevalent in sun-exposed skin and play a crucial role in the early stages of CSCC progression [7,13,14].

Moreover, CSCC frequently exhibits mutations that activate the alpha catalytic subunit of phosphatidylinositol-4,5-bisphosphate 3-kinase (PIK3CA) and the p21 transforming protein (HRAS), as well as mutations in transforming growth factor beta receptors (TGFBR1 and TGFBR2). The transforming growth factor beta signaling pathway has a dual role in CSCC progression, initially functioning as a tumor suppressor but potentially becoming oncogenic at later stages [7,13,14].

SCCs often exhibit mutations or amplifications in receptor tyrosine kinase genes, such as epidermal growth factor receptor, fibroblast growth factor receptor 3, tyrosine-protein kinase, and receptor tyrosine-protein kinase (ERBB4), leading to uncontrolled cell proliferation [15,16].

The expression of molecules associated with epithelial-mesenchymal transition, such as E-Cadherin and Syndecan-1, is also relevant. Figure 1 depicts various genes and molecules.

As described, these genes are not deregulated initially; their deregulation occurs with increasing tumor aggressiveness [15,16].

Several studies have highlighted the wide range of mutations involved in the pathogenesis of CSCC, reflecting the complexity of its molecular landscape. Beyond these mutations, CSCC also exhibits other genetic and epigenetic alterations that add to the disease's intricate nature. Consequently, research has increasingly concentrated on understanding the mechanisms underlying this type of cancer to identify factors that can clarify its progression and inform the development of new therapeutic approaches [15–17].

The tumor microenvironment is equally important in the carcinogenesis of CSCC due to the presence of cancer-associated fibroblasts and tumor-associated macrophages, which significantly influence tumor progression, invasion, metastasis, and response to chemotherapy. The extracellular matrix also plays a vital role by providing structural support to the skin and interacting with SCC cells, affecting the cellular processes involved in tumor progression [7,13,14].

In summary, the development of CSCC is a complex process driven by the accumulation of genetic and epigenetic abnormalities. UV radiation is a key factor contributing to the high mutation rates observed in these tumors. Ongoing research efforts are focused on enhancing our understanding of CSCC biology, aiming to develop more effective therapeutic strategies and interventions [7,14].

## SYNDECAN-1 (SDC1 OR CD138)

### Structure and function

Syndecans are type I transmembrane proteoglycans composed of four isoforms: Syndecan-1 (SDC1 or CD138), Syndecan-2 (SDC2 or fibroglycan), Syndecan-3 (SDC3 or N-Syndecan), and Syndecan-4 (SDC4, amphoglycan or ryudocan) [18–22]. Each isoform has a central protein structure that varies in the number of attached glycosaminoglycan

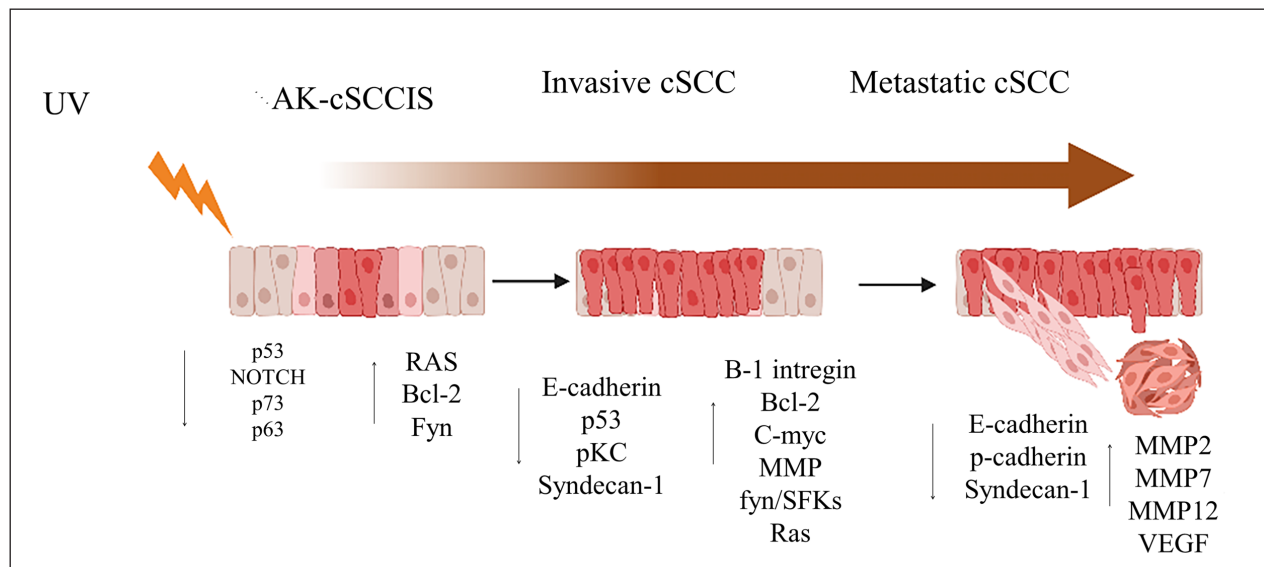
(GAG) side chains and is expressed in different cells, levels, and locations depending on the developmental stage [18,23,24].

Syndecan-1 (SDC1), encoded by the *CD138* gene, has been extensively studied. During development, SDC1 is located on the basolateral surface of epithelial cells and in plasma cells, fibroblasts, and mesenchymal cells. Syndecan-2 (SDC2) is primarily found in endothelial and mesenchymal cells, Syndecan-3 (SDC3) in cells derived from the neural crest, and Syndecan-4 (SDC4) is ubiquitously expressed at lower levels across nearly all cell types [5,20].

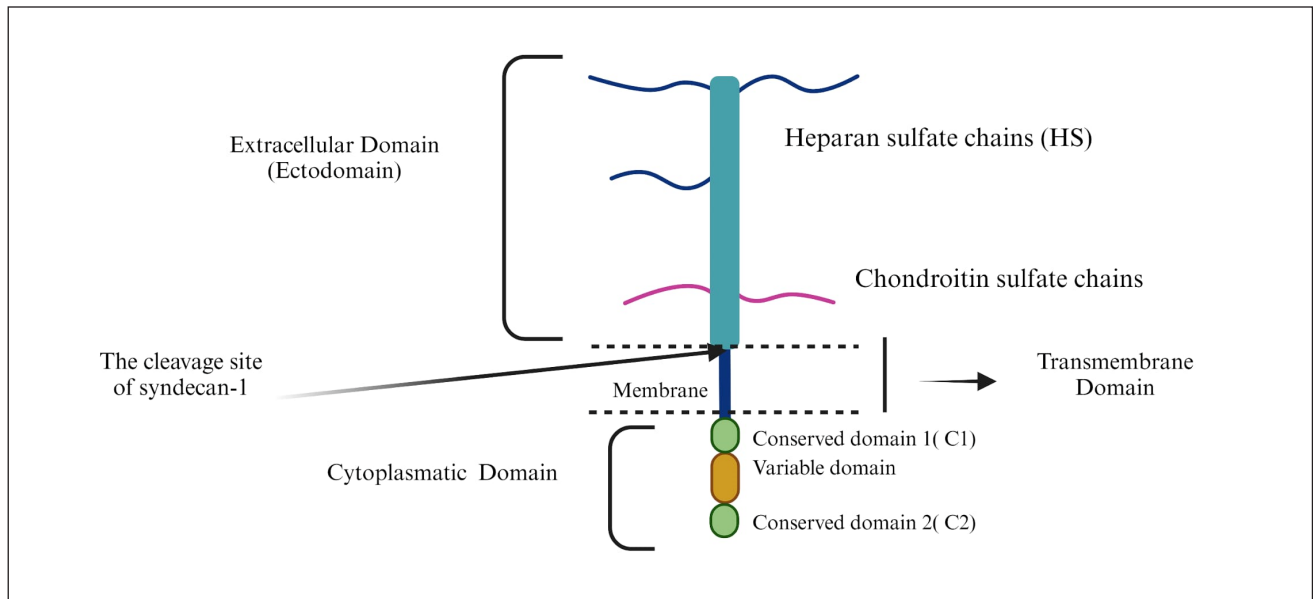
SDC1 regulates cell adhesion, extracellular matrix composition, cell migration, and growth. It is detected in various tissues, including the skin, oral cavity, tonsils, lips, salivary glands, gastrointestinal tract (esophagus, stomach, and intestine), gallbladder, pancreatic duct cells, hepatocytes, urogenital system, respiratory system, and female reproductive organs [5,6,23,25,26]. SDC1 has a unique structure consisting of extracellular, transmembrane, and cytoplasmic domains. The extracellular domain contains covalently linked GAG chains, primarily heparan sulfate (HS) and chondroitin sulfate [18]. The cytoplasmic domain is divided into C1, C2, and a variable (*V*) region. The functions of SDC1 can vary significantly depending on the tissue type and the stage of cell development, as illustrated in Figure 2 [27–30].

The GAG chains of SDC1 facilitate interactions with various molecules crucial for intercellular signaling and the maintenance of cell morphology. As a reservoir for growth factors or as a co-receptor for signal transduction, SDC1 is vital for the function of epithelial cells. Despite being the most extensively studied isoform, much remains to be understood about its full range of functions [27,31].

The synthesis of SDC1 begins in membrane-bound ribosomes and is followed by its translocation to the endoplasmic reticulum. In the Golgi apparatus, GAG chains are covalently attached to the core protein, modifying the structure of SDC1.



**Figure 1.** Molecular changes associated with the progression from AK (a precancerous lesion) to invasive CSCC, [15].



**Figure 2.** Structure of Syndecan-1 with three domains: the extracellular domain, the transmembrane domain and the cytoplasmic domain. The arrow indicates where the cleavage of the ectodomain occurs, resulting in its elimination, [33].

The modified SDC1 is then transported to the cell surface via exocytosis [29,32].

SDC1 acts as a co-receptor on the cell surface, facilitating interactions between ligands and their signaling receptors, such as VEGF, WNT, and HGF [29,33–35]. Additionally, proteolytic cleavage of the extracellular domain near the plasma membrane releases a soluble form of the proteoglycan that retains the heparan sulfate chains. This soluble form of Syndecan-1 can either remain in solution or bind to and accumulate in the extracellular matrix [33,35].

Several mechanisms regulate the elimination of Syndecan-1. The phosphorylation of tyrosine residues in the cytoplasmic domain and the interaction between the cytoplasmic domain and Rab5 control this process. Moreover, bacterial virulence factors, insulin, and oxidative stress can also influence the elimination of Syndecan-1 [36,37]. Heparanases can weaken the binding of the core protein, facilitating cleavage, while matrix metalloproteinases (MMPs), when activated, can shed the SDC1 ectodomain, as shown in Figure 3 [28,36–40].

Soluble SDC1 and membrane-bound SDC1 exert opposing effects on cancer cells, influencing metastasis, tumor growth, chemokine localization, and leukocyte trafficking. When SDC1 translocates to the nucleus or stroma, it is associated with various pathological effects. Elevated levels of soluble SDC1 have been linked to conditions such as inflammation, sepsis, lung diseases, coagulopathies, pulmonary embolism, and tumor invasion [41,42].

#### SDC1 expression in CSCC

SDC1 is the most extensively studied among the four Syndecans due to its critical role in tumor progression, particularly in epithelial cancers such as breast carcinoma [43], Oral SCC [44], and head and neck SCC [45]. SDC1 is essential for maintaining cell cohesion; when epithelial cells

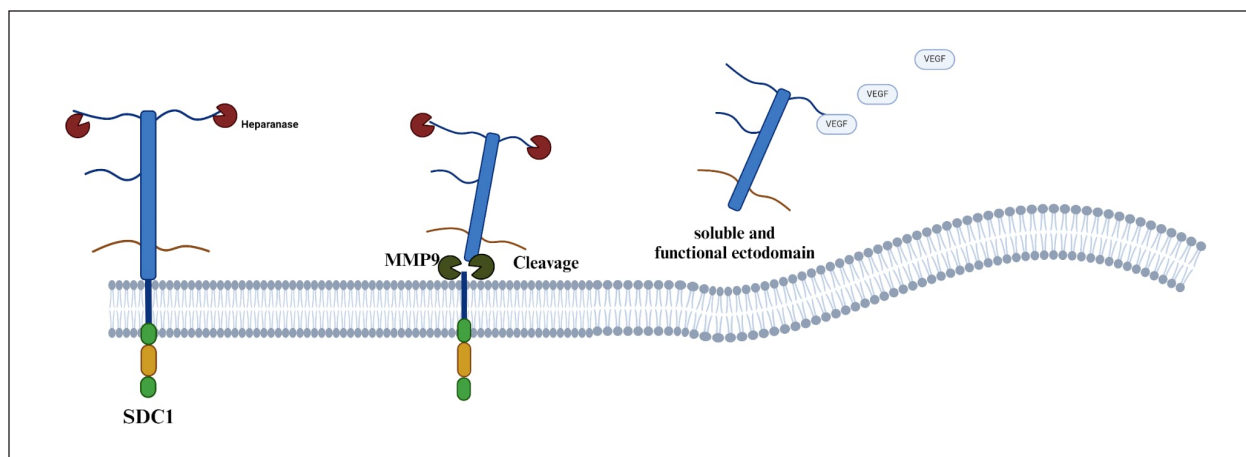
lose SDC1 expression, they lose their cuboidal shape, adopt a mesenchymal phenotype, and gain migratory and invasive properties. Reduced expression of SDC1 has been observed in several types of carcinomas, including CSCC [46,47].

In CSCC, the role of SDC1 has been relatively understudied in humans and dogs. However, existing research indicates a decrease in SDC1 levels in invasive CSCC, which correlates with tumor differentiation, reinforcing its role as a prognostic marker, as observed in other forms of SCC [48–50]. This reduction may result from transcriptional deregulation or the shedding of the SDC1 ectodomain, driven by constitutive MMPs [51].

In addition to the intensity of SDC1 expression in tumor cells, its nuclear or stromal localization should also be evaluated, as these locations are associated with poor prognosis in some tumors. However, the nuclear localization of soluble SDC1 and its functional significance is not yet fully understood [52–55]. When SDC1 translocates to the nucleus, it can influence gene expression through several mechanisms, such as regulating the transcription machinery by inhibiting DNA topoisomerase, which prevents DNA relaxation and access to transcription factors [56]. SDC1 can also modulate gene expression by altering the acetylation states of histone proteins, thereby impacting tumor behavior [18,34,57]. The HS chains in the SDC1 ectodomain bind to growth factors and other regulatory proteins, suggesting that SDC1 may transport these molecules to the nucleus. The cleavage of CD138 by heparanase can lead to gene activation. This nuclear translocation may also regulate epithelial-mesenchymal plasticity, influencing epithelial-mesenchymal transition and the invasive behavior of tumor cells [18,34,58].

In several human cancers, including breast, gastric, ovarian, and oral carcinomas, stromal SDC1 promotes epithelial cell proliferation. Stromal SDC1 expression has also been





**Figure 3.** Illustration of the elimination of SDC1 by MMP9. Once SDC1 becomes soluble, it can bind to various molecules and potentially influence cancer progression. [29].

observed in SCC [59]. Stromal SDC1 expression facilitates tumor cell invasion and motility during tumor progression and has been correlated with clinicopathological parameters and, consequently, a poor prognosis. This stromal source of proteoglycan may originate from cancer-associated fibroblasts [42].

It is also believed that this variation in SDC1 localization may be related to the occurrence of metastases. Heparanase facilitates the shedding of SDC1, leading to increased levels of MMPs and, consequently, a higher incidence of metastasis [26,60].

### Therapies associated with SDC-1

As outlined, SDC1 is expressed in CSCC and is considered a potential prognostic biomarker for the disease. Developing new therapies targeting this marker has been a significant focus of recent research [61,62]. One promising approach involves inactivating molecules that facilitate the elimination of Syndecan-1, as this process plays a crucial role in tumor progression. Heparanase, a molecule associated with poor prognosis and increased metastasis, promotes the elimination of SDC1 and has become a target for new therapeutic strategies [63]. Inhibiting heparanase has successfully reduced invasiveness in human osteosarcomas [64].

Thus, a promising strategy for CSCC involves inhibiting heparanase using modified heparins and small molecule inhibitors and blocking monoclonal antibodies. Heparanase cleaves the heparan sulfate chains of SDC1 at specific sites, and its inhibition reduces the degradation of SDC1. Although heparin acts as a heparanase inhibitor, its clinical use in cancer therapy is limited due to its anticoagulant effects. However, combination therapies with heparin are currently being developed and are widely utilized [64].

Another promising target related to SDC1 is MMPs. The combined clinical application of MMP inhibitors with chemotherapy may offer an effective strategy to prevent the degradation of SDC1 and the creation of microenvironments conducive to tumor recurrence. As mentioned, chemotherapy can increase the elimination of Syndecan-1 by promoting the

production of MMPs, which are zinc-containing endopeptidases secreted by keratinocytes in response to stimuli such as UV radiation [21]. Therefore, the use of MMP inhibitors can reduce Syndecan-1 shedding. An example of such an inhibitor is Batimastat (BB-94), which prevents SDC1 degradation, reduces ascites, and disrupts carcinogenesis in breast, ovarian, and colorectal cancers [28,65].

Therefore, the literature suggests that an ideal therapeutic approach combines chemotherapy with agents that decrease the elimination of SDC1 [28,40]. Additionally, therapies that target growth factors binding to SDC1 and disrupt these interactions to reduce malignancy are of interest. For example, in breast cancer, syntetin—a peptide mimetic of Syndecan docking motifs—interferes with the interactions between integrins, IGFR1, VEGFR, and SDC1, leading to a significant reduction in angiogenesis and tumorigenesis *in vivo* [28].

Another promising approach involves using the soluble form of SDC1, which functions as a tumor suppressor capable of inhibiting tumor growth. To leverage this property, analogs of SDC1 have been developed by attaching GAG chains to a protein framework, creating synthetic proteoglycans. These synthetic proteoglycans have shown the ability to inhibit the viability of myeloma cells both *in vitro* and *in vivo* in a murine model of breast cancer [51].

A proposed therapy involves the overexpression of the C-terminal fragment of SDC1, which may suppress tumor cell migration and invasion. This fragment has been demonstrated to inhibit tumor cell migration and increase basal phosphorylation of Src and FAK. Although these therapies have been primarily investigated in breast cancer and myeloma, no specific therapies targeting CSCC have been described [36].

One study investigated the role of the microRNA miR-10 and found that miR-10 inhibitors decreased the SDC1 expression. This study, therefore, serves as an example of a possible therapy associated with *sdcl* expression, thus focusing on solving inhibitors of molecules that cause SDC1 to decrease [66].

## CONCLUSION

As mentioned, Syndecan-1 plays a complex role in cancer, particularly in SCC, where its deregulation has been observed, although few studies on the subject exist. Beyond its typical membranous localization, Syndecan-1's abnormal expression in the nucleus and its presence in the stroma is also significant from a pathological perspective.

Since tumor malignancy is generally linked to reduced expression of syndecan-1, therapies often focus on preventing the loss of Syndecan-1, which can help slow tumor progression. Investigating the mechanisms behind Syndecan-1 loss could be valuable for developing future therapies for SCC.

Therefore, further studies are needed to enhance our understanding of Syndecan-1 expression in this type of cancer. This could provide important insights into tumor progression and pave the way for new therapeutic approaches.

## AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the international committee of medical journal editors (ICMJE) requirements/guidelines.

## FINANCIAL SUPPORT

This work was supported by the projects UIDB/00772/2020 (Doi:10.54499/UIDB/00772/2020) funded by the Portuguese Foundation for Science and Technology (FCT).

## CONFLICTS OF INTEREST

The authors report no financial or any other conflicts of interest in this work.

## ETHICAL APPROVALS

This study does not involve experiments on animals or human subjects.

## DATA AVAILABILITY

All data generated and analyzed are included in this research article.

## PUBLISHER'S NOTE

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## USE OF ARTIFICIAL INTELLIGENCE (AI)-ASSISTED TECHNOLOGY

The authors declares that they have not used artificial intelligence (AI)-tools for writing and editing of the manuscript, and no images were manipulated using AI.

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**How to cite this article:**

Files R, Cardoso C, Prada J, Silva F, Pires I. Syndecan-1 as a therapeutic target in squamous cell carcinoma: Current insights and future directions. *J Appl Pharm Sci*. 2025;15(02):037–044.