

Review Article

Role of RUNX2 in Oral Squamous Cell Carcinoma (OSCC): A Systematic Scoping Review

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RUNX2, known as the core-binding factor subunit alpha-1 (Cbfa1), is a protein-coding gene recognized and responsible for its involvement in bone development and osteoblast differentiation. However, its dysregulation and aberrant expression have been linked to the pathogenesis of many diseases, such as oral squamous cell carcinoma (OSCC). This review highlights the significance of the RUNX2 gene in oral squamous cell carcinoma. *Objectives.* To review the contribution of the RUNX2 gene in oral squamous cell carcinoma and its implication on clinical diagnosis and treatments. *Materials and Methods.* A systematic scoping review was conducted to elucidate the role of RUNX2 in OSCC. A framework of five stages for scoping reviews outlined by Arksey and O'Malley (2005) was adopted for the current study. *Results.* The review showed that RUNX2 plays a role in the development and progression of OSCC, a common form of head and neck cancer. *Conclusion.* RUNX2 is an essential player in the molecular mechanisms underlying the development and progression of oral squamous cell carcinoma, and its dysregulation promotes tumor initiation, progression, and metastasis, making it a potential target therapy for future research aimed at developing novel therapies for oral squamous cell carcinoma. *Clinical Relevance.* Understanding the precise mechanisms by which RUNX2 contributes to OSCC pathogenesis can lead to target treatment for this challenging form of cancer.

1. Introduction

RUNX2, known as core binding factor alpha 1 subunit (Cbfa1), *Pebp2 α A* is a member of the RUNX family of transcription factors, which are characterized by their DNA-binding domains, known as the Runt domains [1]. RUNX2 is a transcription factor protein that is essential for bone formation and is known to play an important role in various other biological processes [2].

In bone formation, RUNX2 is a master regulator of osteoblast differentiation and bone formation. It has been shown to be essential for the responsibility of mesenchymal stem cells to the osteoblast lineage, as well as for the differentiation of preosteoblasts into mature osteoblasts [3]. RUNX2 is also involved in the mineralization of bone matrix and the regulation of bone remodeling (Figure 1) [3, 4]. RUNX2 is also involved in other biological processes,

including the regulation of tooth development, chondrogenesis, and the maintenance of the hematopoietic stem cell [5, 6]. In addition, it has been shown to play a role in the regulation of angiogenesis and tumor metastasis [7].

Osteoblasts produce and mineralize the extracellular matrix of bone, essential for maintaining skeletal integrity. RUNX2 activates the expression of various genes involved in osteoblast differentiation, including alkaline phosphatase (ALP), osteocalcin (OCN), and collagen type I (COL1A1) [8]. Furthermore, RUNX2 is also involved in maintaining bone homeostasis and remodeling by regulating osteoclast differentiation and activity [9]. RUNX2 is also implicated in chondrogenesis, the process by which cartilage is formed. In chondrocytes, RUNX2 plays a role in regulating the expression of genes involved in chondrocyte differentiation, such as type II collagen (COL2A1) and aggrecan (ACAN) [10, 11]. Additionally, RUNX2 is involved in developing craniofacial bones and teeth [12].

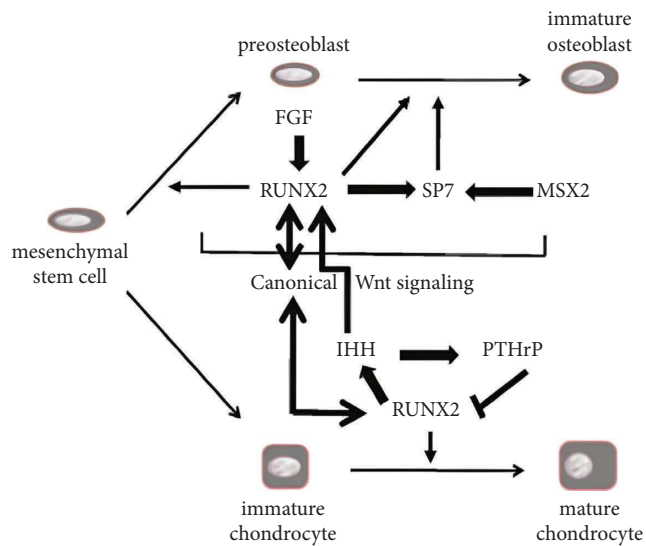


FIGURE 1: Summarize RUNX2 role of regulation and differentiation in mesenchymal stem cells for osteoblast cells and contribution to chondrocyte maturation [40].

RUNX2 is a critical factor in bone formation and other biological processes, and its dysregulation has been implicated in a variety of skeletal and nonskeletal diseases [13]. For example, mutations in the RUNX2 gene have been associated with cleidocranial dysplasia, a skeletal disorder characterized by abnormal bone development [14]. RUNX2 has also been implicated in developing and progressing breast and prostate cancer [15, 16]. The function of RUNX2 is regulated by a variety of signaling pathways, including the Wnt, BMP, FGF, Shh, and PTH pathways [4], and RUNX2 activity is also modulated by posttranslational modifications, including phosphorylation, acetylation, and SUMOylation [17]. Runx2-dependent transcription is regulated by post-translational modifications and interactions with additional nuclear factors. The key components involved in these modifications include chromatin remodelers such as the Swi/Snf complex [18], ATPase proteins Rvb1 and Rvb2 [19], and histone 3 lysine 9 (H3K9) demethylases like JMJD2d/Kdm4d [20]. The Swi/Snf complex is required for cotranscriptional nucleosome remodeling, leading to transcriptional interference and repression of gene expression [21]. Rvb1 and Rvb2 proteins are enriched at gene promoters and mRNAs, where they sequester mRNAs into mRNP granules and repress their translation [22]. JMJD2d/Kdm4d demethylase regulates type I interferon responses by affecting the transcription of enhancer RNAs (eRNAs) and dynamic H3K9me2 at associated promoters. These components play crucial roles in regulating Runx2-dependent transcription through various mechanisms, including chromatin remodeling, mRNA localization, and translatability. The main driving components that play a major role in dysregulation and aberrant expression of RUNX2 in cancer are several. One mechanism involves the cooperation of enhancers and chromatin looping, which is controlled by the transcription factor c-JUN and the epigenetic regulator BRD4 [23]. Another mechanism involves the activity of histone deacetylases (HDACs), particularly HDAC1 and

HDAC6, which are required for efficient transcription of RUNX2 in cancer cells [24]. Additionally, constitutive activation of signaling pathways, such as ERK, Smads, cdk, and Akt, can lead to aberrant expression and activation of RUNX2 [24]. Treatment with histone deacetylase inhibitors (HDACi) can inhibit RUNX2 expression by disrupting the transcription-activating complex on the enhancer element within the RUNX2 gene [25]. These findings suggest that dysregulation and aberrant expression of RUNX2 in cancer can result from a combination of enhancer-mediated chromatin looping, epigenetic regulation by HDACs, and activation of signaling pathways. Recent studies have suggested that RUNX2 may also have a role in cancer. In particular, RUNX2 has been found to be overexpressed in various types of cancer, including breast, prostate, and lung cancer [15, 26, 27]. RUNX2 is thought to promote tumor growth and metastasis by inducing the expression of genes involved in angiogenesis, cell migration, and invasion. A study by Yang DP et al. (2020) found RUNX2 was overexpressed in lung squamous carcinoma and correlated with the clinical progression of this fatal disease [27].

Dysregulation and aberrant expression of RUNX2 have been linked to the pathogenesis of OSCC. Its dysregulation promotes tumor initiation, progression, and metastasis [28]. Head and neck squamous cell carcinoma (HNSCC) is the sixth most common cancer globally, and OSCC is the most common malignant type of HNSCC [29, 30]. Cancer is a leading cause of death globally, accounting for one in six deaths or nearly 10 million in 2020 [31]. With recent scientific advances in cancer detection and treatment, the survival rate of many cancer types has witnessed tremendous improvement. However, HNSCC has a poor survival rate with the 5-year survival rate at an abysmally low level of 50%. Recurrence and metastasis are the main reasons for the poor survival rate [32]. Recurrence occurs in about half of all HNSCC patients [33]. Hence, novel therapeutic strategies aimed at controlling recurrence and metastasis can go a long way in improving the prognosis and survival rate of the patients.

This review systematically identified evidence from the recent research studies on the role of RUNX2 in HNSCC. It explored the possibility that RUNX2 could be used as a biomarker for the prognosis of OSCC. The prevailing perception and scope of development of therapeutic strategies using RUNX2 to treat OSCC are emphasized.

2. Methodology

Before the advent of the current review, a preliminary search of MEDLINE, the Web of Science, and JBI Evidence Synthesis was conducted, and no current or ongoing systematic reviews or scoping reviews on the topic were identified. The current scoping review was conducted following the framework designed by Arksey and O'Malley following the 5-step framework [34].

2.1. Identifying the Research Question

- (i) The main research question was "What is the role of RUNX2 in oral squamous cell carcinoma?" the

TABLE 1: MEDLINE search terms (14/12/2023).

Search terms	MeSH terms	Text words
RUNX2	Core-binding factor alpha 1 subunit (MeSH) Core-binding factor alpha 1 subunit (SH) "RUNX2 protein, human" (supplementary concept)	RUNX2 (tiab) Core-binding factor alpha 1 subunit (tiab)
OSCC/HNSCC	Squamous cell carcinoma of head and neck (MeSH) Squamous cell carcinoma of head and neck (SH)	Squamous cell carcinoma of head and neck (tiab) Oral squamous cell carcinoma (tiab) Oral cancer (tiab) Head and neck cancer (tiab)

subquestions were "What are the types of studies conducted on the role of RUNX2 in OSCC?" "Does RUNX2 have any prognostic or therapeutic role in OSCC?" and "What are the gaps in the literature available on this topic?".

(ii) Identifying relevant studies

Following the PCC (population, concept, and context) criteria, with the population being OSCC and HNSCC patients and the concept being the role of RUNX2, relevant studies were identified using specific eligibility criteria. Only original research articles published in peer-reviewed journals and in English language were considered for the review. Preprints were excluded. An elaborate scientific literature search was executed with no start date restriction until 8 September 2023 in the electronic databases MEDLINE, Web of Science, and Scopus, following specific eligibility criteria. The protocol for search terms and the search strategy used for MEDLINE and Web of Science is given in Tables 1–3, respectively.

2.1.1. Selection of Studies for Inclusion. The results of the search and the study inclusion process are presented in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for scoping review (PRISMA-ScR) flow diagram (Figure 2) [35]. After reading through the title and abstract of the articles, one article was excluded for being a meeting abstract, whose full text was not available online. After full-text screening was performed, two articles were excluded because they were not appropriate for the review. Finally, seven articles were included in this review. Following the search, all identified citations were collated and uploaded into EndNote version 21, and duplicates were removed. Titles and abstracts were screened for assessment against the inclusion criteria for the review. A total of 10 studies were selected by this method.

2.1.2. Data Extraction and Charting of Data. After a thorough reading of the selected articles, the required data were extracted and entered into MS word. The collected data included authors, date of publication, study type, study population, and key points to be taken from the study (Table 3). The data were regularly updated and meticulously charted.

2.1.3. Collating, Summarizing, and Reporting of Results. A thorough summary of the results was prepared, and a narrative approach is used to report the results of this systematic scoping review using figures and tables [34, 36].

3. Results and Discussion

The result of the review is given in Table 3. The role of RUNX2 in OSCC was thoroughly studied and summarized legibly in this review.

3.1. RUNX2 and OSCC. High RUNX2 expression levels have been observed in OSCC tissues and are associated with tumor growth, invasion, and metastasis. RUNX2 interacts with several signaling pathways involved in OSCC pathogenesis, such as the Hedgehog signaling pathway. Zhang et al. mentioned that RUNX2 promoted fibroblast activation and OSCC cell proliferation and migration [28]. It is a multipotent transcription factor that regulates various genes and interacts with different oncogenic transcription factors of HNSCC, like TP53, JUN, and HIF-1A [37–40].

RUNX2 plays a major role in tumor cells' transformation, growth, metastasis, cachexia, and hypercalcemia [7, 41]. RUNX2 crosstalks with other transcription factors to regulate the function of oncogenes and cancer progression. It also has a prometastatic function, playing a significant role in the cervical metastasis in HNSCC [23]. In HNSCC, RUNX2 collaborates or engages in crosstalk with other transcription factors to regulate oncogenes' functions and influence the progression of cancer [23]. Chang et al. found that in HNSCC, RUNX2 could have a specific transcription target and demonstrated the prometastatic function of RUNX2 [23].

Increased expression of RUNX2 following the knock-down of tumor suppressor microRNA, miRNA-376c-3p, leads to an upregulation of invasive and migratory abilities of tumor cells and increased infiltration of cervical lymph nodes [23].

3.2. RUNX2 as a Prognostic Biomarker. RUNX2 has been linked to the development of metastasis in various cancers. In OSCC, its expression may be associated with an increased risk of lymph node metastasis [23]. Therefore, assessing RUNX2 levels could aid in predicting the likelihood of metastasis and tailoring treatment strategies accordingly.

Wen et al. identified RUNX2 as one of the most tumor-specific markers for hepatocellular carcinoma (HCC) [48]. The methylation levels of RUNX2 showed a strong positive correlation with tumor size and could differentiate between cancer patients and controls, enabling sensitive detection. RUNX2 was one of the markers that provided a more specific indication of HCC presence [48].

TABLE 2: MEDLINE search strategy.

Search number	Query	Search details	Results
1	("RUNX2 protein, human" (supplementary concept)) OR "core binding factor alpha 1 Subunit" (Mesh)	"RUNX2 protein human" (supplementary concept) OR "core binding factor alpha 1 Subunit" (MeSH terms)	4,743
2	(RUNX2 [Title/Abstract]) OR (core binding factor alpha 1 subunit [title/Abstract])	"RUNX2" (Title/Abstract) OR "core binding factor alpha 1 subunit" (Title/Abstract)	10,170
3	#1 OR #2	"RUNX2 protein human" (supplementary concept) OR "core binding factor alpha 1 Subunit" (MeSH terms) OR "RUNX2" (Title/Abstract) OR "core binding factor alpha 1 Subunit" (Title/Abstract)	11,106
4	"Squamous cell carcinoma of head and Neck" (Mesh)	"Squamous cell carcinoma of head and Neck" (MeSH terms) (("Epithelial cells" (MeSH terms) OR "epithelial" (All fields) AND "cells" (All fields)) OR "epithelial cells" (All fields) OR "Squamous" (All fields) AND "Cell" (All fields)) OR "squamous cell" (All fields) AND "carcinoma of head neck" (Title/Abstract) OR "oral squamous cell carcinoma" (Title/Abstract) OR "oral cancer" (Title/Abstract) OR "head neck cancer" (Title/Abstract)	11,582
5	(((((Squamous cell carcinoma of head neck (Title/Abstract)) OR (oral squamous cell carcinoma (Title/Abstract)))) OR (head neck cancer (Title/Abstract)))	"Squamous cell carcinoma of head and Neck" (MeSH terms) OR (((("epithelial cells" (MeSH terms) OR "epithelial" (All fields) AND "cells" (All fields)) OR "epithelial cells" (All fields) OR "Squamous" (All fields) AND "Cell" (All fields)) OR "squamous cell" (All fields) AND "carcinoma of head neck" (Title/Abstract) OR "oral squamous cell carcinoma" (Title/Abstract) OR "oral cancer" (Title/Abstract) OR "head neck cancer" (Title/Abstract))	27,079
6	#4 OR #5	"Squamous cell carcinoma of head and Neck" (MeSH terms) OR (((("epithelial cells" (MeSH terms) OR "epithelial" (All fields) AND "cells" (All fields)) OR "epithelial cells" (All fields) OR "Squamous" (All fields) AND "Cell" (All fields)) OR "squamous cell" (All fields) AND "carcinoma of head neck" (Title/Abstract) OR "oral squamous cell carcinoma" (Title/Abstract) OR "oral cancer" (Title/Abstract) OR "head neck cancer" (Title/Abstract))	36,162
7	#3 AND #6	("RUNX2 protein human" (supplementary concept) OR "core-binding factor alpha 1 subunit" (MeSH terms) OR "RUNX2" (Title/Abstract) OR "core-binding factor alpha 1 subunit" (Title/Abstract)) AND ("squamous cell carcinoma of head and neck" (MeSH terms) OR (((("epithelial cells" (MeSH terms) OR "epithelial" (All fields) AND "cells" (All fields)) OR "epithelial cells" (All fields) OR "squamous" (All fields) AND "Cell" (All fields) OR "squamous cell" (All fields) AND "carcinoma of head neck" (Title/Abstract) OR "oral squamous cell carcinoma" (Title/Abstract) OR "oral cancer" (Title/Abstract) OR "head neck cancer" (Title/Abstract)))	8

TABLE 3: Web of Science search strategy.

Search number	Search	Hits
#1	(TS = (RUNX2)) OR TS = (core-binding factor alpha 1 subunit)	11,513
#2	(TS = (squamous cell carcinoma of head and neck)) OR TS = (oral squamous cell carcinoma) OR TS = (oral cancer)	149,632
#3	#1 AND #2	32

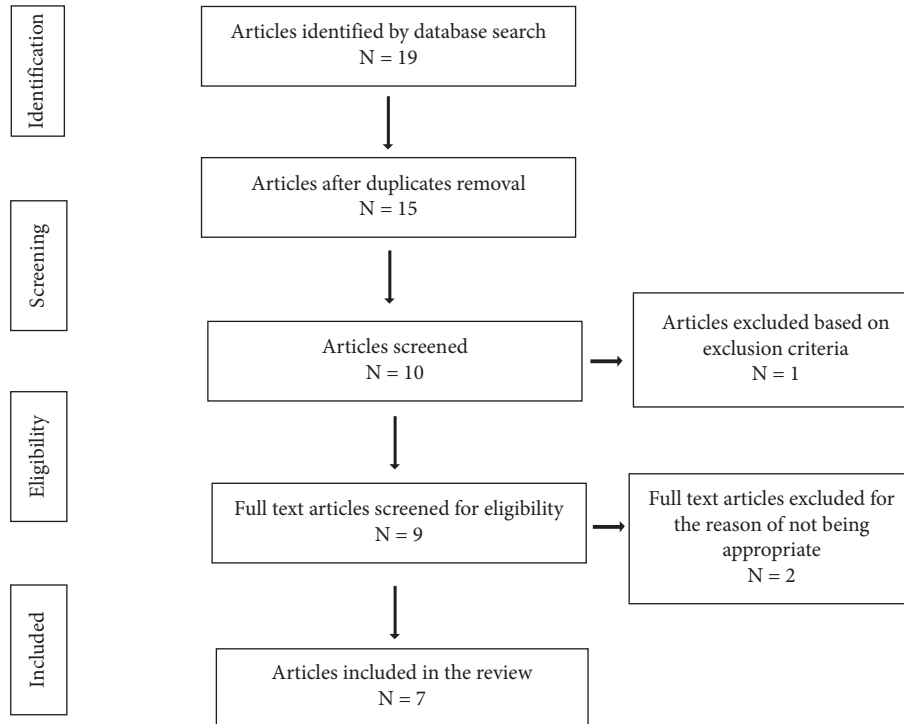


FIGURE 2: PRISMA-ScR flow diagram for studies included in the review.

It is also an independent prognostic biomarker of gastric cancer, linked with the invasion and differentiation of gastric cancer [42].

MicroRNA miR-376c, which inhibits the metastasis of tumor cells in OSCC, suppresses RUNX2 expression [23]. High RUNX2 expression levels were linked with unfavorable prognosis in OSCC patients, indicating the potential use of RUNX2 as a prognostic biomarker. Several studies have shown that the expression levels of RUNX2 can be used to predict the likelihood of recurrence, metastasis, and survival in OSCC patients [45, 46]. However, further studies and investigations are needed to validate these findings and establish the clinical utility of RUNX2 as a prognostic biomarker.

RUNX2 mRNA and protein levels were found to be elevated in clinical HNSCC cases [45]. A study by Chang et al. showed RUNX2 to stimulate HNSCC via parathyroid hormone-like hormone (PTH1H) and was found to be a poor prognostic marker for HNSCC [45]. It was found that PTH1H, calcium, and RUNX2 form a positive feedback loop in HNSCC, and in HNSCC patients, the RUNX2-PTH1H axis promoted tumor growth [45]. Recent studies show that the most activated upstream

regulator in highly metastatic HNSCC was RUNX2 [23, 49]. RUNX2 was found to promote the proliferation abilities of HNSCC cells in vitro and tumor growth in vivo [45].

MRE11 is crucial for DNA double-strand breaks and is the nuclease component of the RAD50/MRE11/NBS1 DNA repair complex. It is also found to be a critical factor in cancer development [50]. In OSCC, MRE11 expression was associated with increased tumor size, cancer stage, and lymph node metastasis. It also predicted poorer patient survival and radiotherapy resistance [43]. Wang et al. found that MRE11 enhanced tumor proliferation, migration, and invasion, which was mediated by RUNX2 CXCR4, AKT, and FOXA2 [43].

3.3. Targeting RUNX2 for OSCC Therapy. MicroRNAs have several translational uses, including being diagnostic and prognostic biomarkers. MicroRNA miR-23a was found to inhibit invasion, proliferation, and clonogenesis of OSCC cells by inhibiting RUNX2 regulation of the PTEN/PI3K/Akt signaling pathway [42]. Chang et al. suggested that therapeutic targeting of the transcriptional activity of RUNX2 by

TABLE 4: List of studies included.

Authors (Reference)	Date of publication	Study population	Key points
Ma et al. [42]	March 2022	OSCC patients	(i) Inhibition of RUNX2 reduced the malignant progression of oral squamous cell carcinoma CAL-27 and TSCCA (ii) Increased expression of RUNX2 reverses the cancer suppressive effect of miR-23a-3p (iii) miR-23a-3p inhibits the PTEN/PI3K/Akt signaling pathway through RUNX2
Zhang et al. [28]	February 2022	OSCC patients	(i) GDF10 interacts with RUNX2 to promote fibroblast activation which improve OSCC tumor cells growth and migration by activating the TGF β RI/Smad3/ERK pathway
Wang et al. [43]	April 2021	OSCC patients	(i) Positive correlation between MRE11, CXCR4 and RUNX2 in oral cancer tissues (ii) MRE11 promotes EMT and metastasis through RUNX2, CXCR4, AKT, and FOXA2
Khanal et al. [44]	December 2020	Head and neck cancer cell lines	(i) Decreased expression of RUNX2 was observed in human papilloma virus positive head and neck cancer cells while it was not the target of epigenetic regulation
Chang et al. [45]	January 2017	Specimens from HNSCC patients	(i) Deranged RUNX2 expression increased PTHLH expression and promoted proliferation potential
Chang et al. [46]	December 2016	Head and neck squamous cell carcinoma cell lines	(i) RUNX2 has a prometastatic action in HNSCC and causally correlates with the metastatic potential of HNSCC (ii) Downregulation of tumor suppressor microRNA, miRNA-376c-3p promotes invasive and migratory abilities of HNSCC by upregulating RUNX2/INHBA axis
Quan et al. [47]	June 2012	OSCC cell lines	(i) RUNX2 levels were not altered in invasive phenotype of OSCC cells

miR-376c treatment could combat the metastatic progression of HNSCC [23]. An experimental study by Ma et al. found that miR-23a-3p inhibits the malignant progression of OSCC [42].

RUNX2's involvement in the progression of oral cancer makes it a potential therapeutic target. Inhibiting or modulating RUNX2 activity could be explored to suppress tumor growth and metastasis. Targeting RUNX2 may represent a promising therapeutic approach for OSCC treatment. Studies have shown that RUNX2 inhibition using siRNA or small molecule inhibitors suppresses OSCC cell growth, invasion, and metastasis in vitro and in vivo [23]. Moreover, RUNX2 inhibition has sensitized OSCC cells to chemotherapy and radiation therapy. However, more studies are needed to determine the safety and efficacy of RUNX2 inhibition as a therapeutic approach for OSCC.

4. Conclusion

RUNX2 is a critical transcription factor that plays a key role in bone formation and other biological processes. Various signaling pathways and posttranslational modifications tightly regulate its activity. Dysregulation of RUNX2 has been implicated in various skeletal and nonskeletal diseases. Recent studies have implicated RUNX2 in cancer, suggesting a potential therapeutic target for the treatment of cancer, including OSCC. They may serve as a prognostic biomarker and therapeutic target for OSCC treatment.

Elevated levels of RUNX2 expression have been detected in OSCC tissues and are correlated with the growth, invasion, and metastasis of tumors. RUNX2 has been associated with the development of metastasis across various cancers, and in the case of OSCC, its expression may be linked to an increased risk of lymph node metastasis. Consequently, evaluating the levels of RUNX2 could assist in predicting the likelihood of metastasis, guiding treatment strategies accordingly. Moreover, heightened RUNX2 expression has been associated with an unfavorable prognosis in OSCC patients, suggesting the potential utility of RUNX2 as a prognostic biomarker. Given RUNX2's role in the progression of oral cancer, it emerges as a plausible therapeutic target. Exploring the inhibition or modulation of RUNX2 activity could be considered to suppress both tumor growth and metastasis. Therefore, targeting RUNX2 presents a promising therapeutic approach for the treatment of OSCC. There is a dearth of studies analyzing the molecular mechanisms involved in the role of RUNX2 in OSCC. Future studies should further elucidate the molecular mechanisms underlying RUNX2-mediated OSCC pathogenesis and develop safe and effective RUNX2-targeted therapies for OSCC patients.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The author declares that there are no conflicts of interest.

Authors' Contributions

Khalid A. AL-Hamad performed writing of the manuscript and contributed to the main text.

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