LETTER TO EDITOR

Precision Medicine for Oral Cancer: Exploiting the miR-34/SATB2 Regulatory Network

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Dear Editor,

Oral squamous cell carcinoma (OSCC) stands as a significant contributor to global cancer-related mortality and has escalated in recent times. Despite the advancement in technical methodologies for disease localization, grading and staging, approximately 50% of OSCC patients experience frequent recurrences. Various molecular pathways are implicated in the development and progression of OSCC. It is crucial to understand the interactions among these pathways, as well as their significance in the domain of oncology. miRNAs (miRNAs) are single stranded, non-coding RNAs (containing ~20– 22 nucleotides) involved in the regulation of a variety of physiological and pathological scenarios by targeting specific mRNAs involving infection, immunity and carcinogenesis. Among the diverse range of miRNAs, miRNA-34 holds significant importance in cancer progression and metastasis. Regulation at the transcriptional level by different factors is pivotal in managing the levels of miR-34. The tumour suppressor protein p53 directly interacts with the promoter of the miR-34 gene, upregulating the transcription. Additionally, various transcription factors including Elk-1, STAT3, Snail, Slug, ZEB1, and ZEB2 have been associated with the control of miR-34, affecting over 700 genes that are either projected or validated targets of miR-34s. They participate in crucial signalling cascades associated with progression and proliferation of malignant tumours such as p53, MAPK, Notch, Wnt, PI3K/AKT and Ras pathways. Moreover, miR-34s regulate critical mechanisms linked to cancer cell migration, invasion and the process of epithelial-mesenchymal transition (EMT). Previous research has elucidated the significant role of p53/miR-34 interaction in OSCC, where they coordinate changes in the cell cycle and promote EMT. Bypassing mutations or alterations in the epigenetic mechanism to p53 and directly administering miR-34 mimetics represents a prospective interventional approach for a subset of cancers characterized by dysregulated cell cycle checkpoints. Corcoran et al emphasized consistent decrease in miR-34 expression across various cancer types, highlighting its role as a tumour suppressor.

Special AT-rich DNA binding protein (SATB2), an 82.5 kDa protein (733 amino acids), encodes a protein crucial for chromatin remodelling by binding to matrix attachment regions of the nucleus (MARs) and regulates chromatin organization, transcription, and tumorigenesis. The expression of SATB2 varies depending on the embryonic origin of the tissue, developmental phase and are affected by a myriad of cell signals. SATB2 plays multiple roles in craniofacial development, osteoblast differentiation and the initiation and progression of cancer. These varied physiological roles of SATB2 are modulated through ligand-receptor signalling pathways. In various types of carcinomas, SATB2 has shown to exhibit aberrant expression patterns that contribute to tumour metastasis and progression such malignancies often show increased SATB2 expression with low survival rate, whereas colorectal cancer tends to suppress it. An increase in SATB2 protein promotes EMT, which facilitates invasion and metastasis by enabling epithelial cells to acquire mesenchymal characteristics, thus promoting tumour cell dissemination and spread to distant sites. It was reported by Jiang et al that SATB2 protein being upregulated in hepatocellular carcinoma leading to cell proliferation and metastasis, while Wang et al studied the upregulation of SATB2 led reduced of mRNA levels of SNAIL gene in colorectal cancer cells. They further characterized three SATB2-binding motifs within an AT-rich sequence located in the SNAIL promoter region.

miR-34 has been identified as a direct inhibitor of SATB2 expression, exerting negative regulatory control over the SATB2 gene. This regulatory interaction is implicated in modulating crucial cellular processes, including developmental pathways and differentiation cascades. Ge X et al. observed that miR-34a suppressed the invasion and metastasis of OSCC cells by reducing SATB2 expression,[1] Wu G et al investigated the relationship between SATB2 expression and miR-34a, focusing on OSCC found low levels of miR-34a correlated with upregulation of SATB2.[2] They identified SATB2 as a direct target of miR-34a and inferred that miR-34a functions as a tumour suppressor in OSCC by targeting SATB2, thereby inhibiting proliferation and expansion of cancer cells. The precise mechanism concerning the interrelation of SATB2 and miR-34a in this context remains to be fully understood.

Based on prior study findings, we suggest a pathway given in figure 1 involving miR-24 and SATB2 and its implication in EMT event in OSCC. miR-34 molecule acts as a negative regulator of SATB2. Ideally, miR-34 would inhibit the

This article was accepted: 27 September 2024
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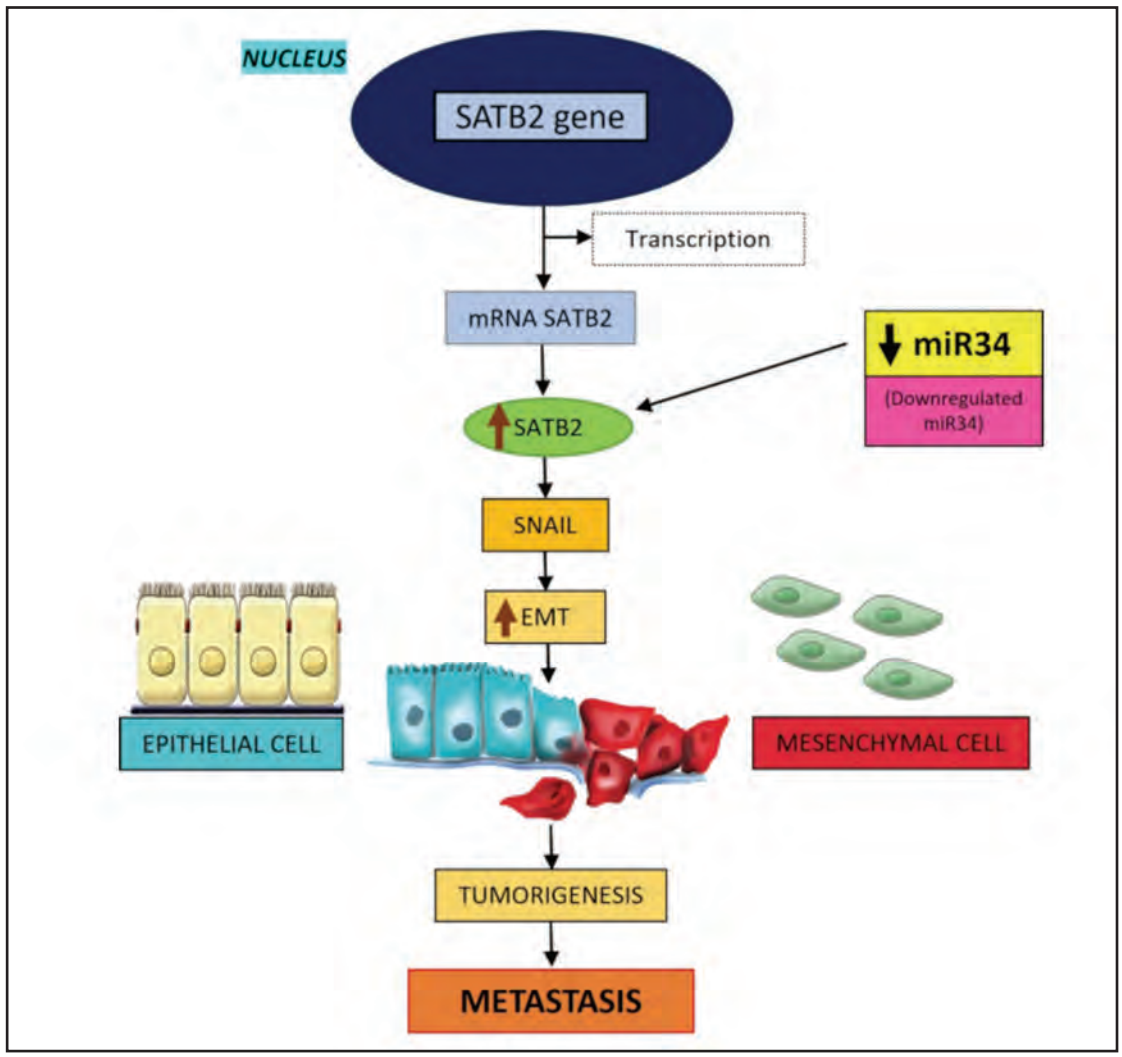

Fig. 1: Schematic illustration of miR34 and SATB2 molecular interaction in the cascade of OSCC tumorigenesis and subsequently metastasis

translation of the SATB2 mRNA into a protein. In the presence of dysregulation, the SATB2 gene is not inhibited by miR34, which can lead to the overexpression of SATB2. This activation results in the production of SATB2 protein, which subsequently upregulates pro- EMT genes such as SNAIL and SLUG. SNAIL serves as a crucial transcription factor in EMT facilitating this process. The overexpression of SATB2 can also contribute to the proliferation of OSCC cells and metastasis. This proposed pathway underscores the intricate molecular mechanisms involved in the progression of OSCC and highlights the potential therapeutic targets within this pathway for future research and intervention strategies. The uncontrolled production of SATB2 protein, due to the lack of miR-34 inhibition, contributes to EMT. Consequently, EMT is associated with the proliferation and metastasis of OSCC cells. With the advent of the first miRNA-based therapy, MIRX34, which delivers a mimic of the tumour suppressor miR-34 encapsulated within SMARTICLES liposomal formulation, there is a unique opportunity to integrate this innovative approach into OSCC (Fig.1). By deciphering the molecular pathway given above the roles of miR-34 and SATB2 in OSCC progression and EMT regulation, future studies could pinpoint precise targets for intervention, potentially leading to more targeted and effective therapies that inhibit metastasis and enhance patient outcomes.

CONFLICT OF INTEREST

There is no conflict of interest.

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