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LETTER TO EDITOR

Nucleostemin and p-STAT3 as early diagnostic potential markers in oral squamous cell carcinoma

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Dear Editor,

Oral cancer is considered the sixth most common type of cancer worldwide, out of which India contributes to about one-third of the total cases [1]. Oral squamous cell carcinoma (OSCC) is the most dominant of all oral cancer cases and may develop from a potentially malignant disorder with a detectable pre-clinical phase. The primary causes of OSCC include tobacco consumption that involves smokeless tobacco, chewing of betel-quid and excessive consumption of alcohol, unhygienic oral practices, periodontal diseases, and sustained viral infections caused by human papillomavirus (HPV) [2]. Instead of these traditional risk factors (alcohol consumption and cigarette smoking), oncogenic HPV is found to be the main causative factor for the increasing incidence of OSCC. Furthermore, HPV etiology is linked to increased survival following conventional treatments.

Clinical studies have revealed that HPV oncogenes are linked to abnormal regulation of STAT (signal transducer and activator of transcription) family proteins that intervenes cellular response to cytokines (including growth factors and IL-6) [3]. STAT3, a transcription factor, has been discovered to be essential for cancer growth. In addition to being constitutively active in cancer cells, it regulates essential cellular processes like self-renewal, survival, and inflammation. STAT3 is phosphorylated at tyrosine 705 and serine 727 in response to a range of hormones, growth factors, cytokines, and protein kinases. To maintain the behavior of a malignant tumor, STAT3 is also constantly activated in several cancer types. The role of STAT3 in chemoresistance and radioresistance is well-known. In addition to their essential role in mediating signaling pathways initiated by receptor and non-receptor tyrosine kinases, these molecules also serve as pivotal transcription factors, exerting control over the expression of a diverse array of genes. This multifaceted function plays a crucial part in driving the progression of tumors [4, 5].

One of the main drivers of OSCC's aggressive approach has been identified as guanine nucleotide-binding protein 3 (GNLP-3) called nucleostemin (NS), which is highly expressed in the nucleolus of neuroepithelial stem cells (central nervous system), embryonic stem cells, primitive stem cells (bone marrow) and cancer stem cells [6]. It is recognized as a promoter for uncontrolled cellular proliferation responsible for tumorigenesis. Additionally, the knockdown of NS significantly inhibits the proliferation of stem cells and cancer cells, suggesting that NS regulates cancer cells. Recently, it was shown that NS, IL-6, and members of its family, Toll-like receptors, G protein-coupled receptors, and microRNAs regulate JAK-STAT signaling in cancer. JAK-STAT3 signaling is well established for its function growth of the tumor cells, invasion, survival, and immunosuppression. It also promotes cancer growth through networking signals involving stem cells, the pre-metastatic niche, and inflammation [4].

High-grade inflammation and a poor prognosis are characteristics of most malignancies. OSCC shows a significant proliferation of NS-positive nucleoli. Since this NS mainly builds up in nucleoli, it flows to the nucleoplasm after interacting with GTP. Apoptosis, cell proliferation, cell cycle regulation, and Self-renewal may all be greatly influenced by NS's interactions with various proteins in the nucleoplasm. As a result, NS expression has been linked to several cancer forms, including squamous cell carcinomas of the head, prostate cancer, esophageal, neck, renal cell carcinomas, and uterine [7]. It was also found that NS overexpression was coupled with STAT3 activation and a poor prognosis in OSCC. For instance, there was a marked and notable rise in the NS signal in poorly differentiated OSCC and high-grade dysplasia. However, phosphorylated STAT3 (p-STAT3) expression was more widespread, and the intensity was consistent in both high-grade dysplasia and in both well and poorly-differentiated OSCC. In order to regulate tumor cell growth, proliferation, differentiation, and metastasis, this p-STAT3 spontaneously dimerizes, migrates into cell nuclei, and triggers the expression of downstream genes. The incidence of prominent nucleolar NS signals significantly increased in instances of low-grade dysplasia that later progressed to OSCC within a 2 to 3-year timeframe, compared to those instances of low-grade dysplasia that remained unchanged over a more extended period of 7 to 14 years in the context of human dysplastic samples. These findings strongly indicate that the initial stages of the conversion from low-grade dysplasia to OSCC involve the overexpression of NS and the activation

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of STAT3. It becomes evident that NS and p-STAT3 may serve as valuable markers for the early detection of OSCC, underscoring their significance as early indicators in both human and rodent oral dysplastic and OSCC lesions [8]. Many malignancies, including OSCC, in which hyperactivation of STAT3 is linked to resistance to both treatment and the immune system, are characterized by aberrant regulation of the STAT3 oncogene, which promotes tumor growth and progression. As the p-STAT3 study has shown, oral leukoplakia patients (with or without dysplasia) and OSCC had higher nuclear p-STAT3 levels [9]. These findings show that p-STAT3 and NS can be used as markers to help with the early detection of precancerous lesions. Therefore, the expression of NS and p-STAT3 suggests that these molecules function as the integrated component that may be implicated in the signaling pathway.

Additionally, they are known to promote the release of cytokines, which in turn causes dysplasia, inflammation, and carcinogenesis [9]. In Figure 1, the functions of NS and p-STAT3 are described. Further experimental research is still needed to recognize better the link between NS and the STAT3 signaling pathway. Two OSCC cell lines that overexpress NS have demonstrated improved invasion and cellular proliferation through the activation of STAT3 signaling in various studies showing NS on the malignant progression of OSCC. Furthermore, it has been demonstrated that advanced primary tumor size nodal status-distant metastasis (TNM) staging results in a worse prognosis for NS in OSCC tissue samples with significant immunological positivity. NS-positive nucleoli are reported to be more extensive than the normal ones [10] despite NS expression not relying on the proliferative status of neoplastic cells.

In static dysplasia, a diffuse pattern of nuclear signals associated with the NS was shown to be highly numerous. In contrast, the nucleolar pattern of NS signals was shown to be more prevalent in progressive dysplasia. Likewise, when examining undifferentiated, rapidly proliferating cells derived from human germ cell tumors and mouse teratoma models, the staining patterns of nucleolar and nuclear NS reveal a striking NS signal concentrated within the nucleolus. This distinctive signal signifies heightened nucleolar activity, primarily associated with the increased production of ribosomes and the orchestration of various other cellular functions unrelated to ribosomal synthesis [10]. In both the growth of embryonic stem cells and the development of cancer, the cell proliferation marker, i.e., NS, plays a crucial role. Overall, these molecules, NS and p-STAT3, influence the release of NS from the nucleolus, increase the production of cytokines, and cause genetic alterations that lead to cancer. They have also been reported to play a regulatory function in advancing oral cancer. In light of the fact that these molecules are able to detect early indications of oral cancer, additional studies on the genetic alterations and the regulation of signaling networks involved *in vivo* are very much essential to develop NS and p-STAT3 as therapeutic targets in OSCC.

Authors' contribution

SJ: Conceptualization, Writing-review and editing
VPV: Writing - original draft

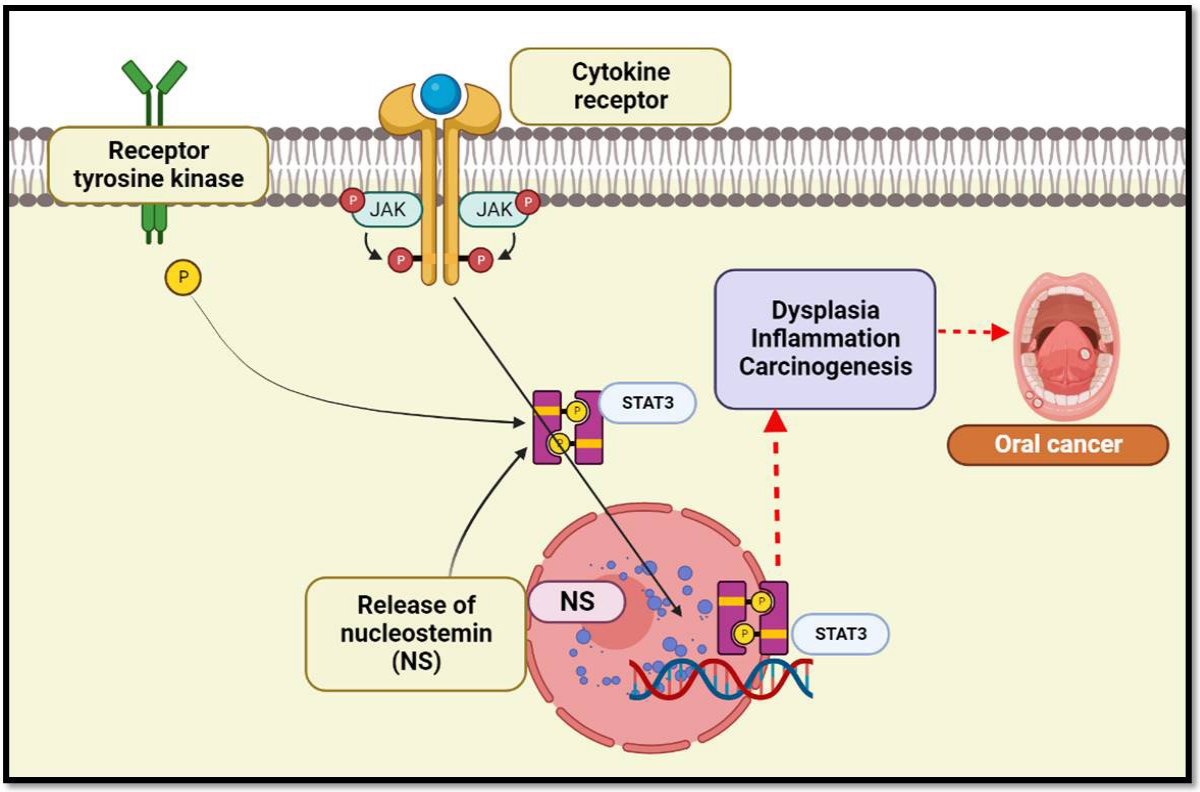

Fig. 1. Role of NS and p-STAT3 in oral cancer.

Conflict of interest

None to declare.

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