Editorial

TSPAN8 and distant metastasis of nasopharyngeal carcinoma cells

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Nasopharyngeal carcinoma (NPC) is an aggressive epithelial carcinoma that is prevalent in Southeast Asia, Southern China and North Africa. It can develop in the presence of various risk factors, including Epstein-Barr virus (EBV) infection, environmental exposure to carcinogens, ethnic background, and genetic predisposition. It is prone to local invasion and early distant metastasis. Patients with early-stage NPC have a relatively high cure rate of over 90% with radical radiotherapy. In contrast, the 5-year overall survival (OS) rate for locally advanced NPC declines to between 50–60% (1). With the combination of intensity-modulated radiotherapy, chemotherapy, surgery and targeted therapy, the locoregional control rate has been reported to be 80–90% in locally advanced NPC, whereas distant metastasis remains the major reason of treatment failure in these patients (2-4). The outcome for patients with distant metastatic NPC is suboptimal, with a median OS of 20 months (5). Unfortunately, roughly 15% NPC patients present with distant metastases at their first diagnosis (6). The understanding of the mechanisms that drive NPC metastasis will be substantially beneficial for developing new and reliable biomarkers for early detection and novel therapeutic strategies for NPC.

The specific molecular mechanisms that drive NPC metastasis remain unclear. The most common histologic type in Eastern countries is undifferentiated carcinoma, while squamous cell carcinoma is more common in USA and Europe. Undifferentiated carcinoma is strongly associated with EBV infection. EBV encodes the oncogene product, latent membrane protein 1 (LMP1). LMP1 executes its oncogenic functions via activating the P38 MAPK signaling pathway, and subsequently decreasing the sensitivity of NPC cells to ionizing radiation (7). Moreover, LMP1-mediated metabolic reprogramming activates IGF1-mTORC2 signaling pathway, facilitates PDHE1α nuclear translocation that leads to acetylation and activation of the Snail promoter (8). However, no efficient EBV targeted therapy has been developed in NPC treatment. Intriguingly, noncoding RNAs, including microRNAs and long noncoding RNAs, are increasingly implicated and appreciated as playing critical roles in the mediation of NPC metastasis (9-12).

In this Journal, Lin *et al.* reported an association between Tetraspanin 8 (TSPAN8) and distant metastasis of NPC (13). There was 1,787 differential expressed genes between paired tumor tissues and benign adjacent tissues from NPC with 8 genes that were highly upregulated in NPC tissues. However, only TSPAN8 is over-expressed in the poorly differentiated CNE2 cell line and the highly metastatic subclone S18 NPC cell line. More importantly, TSPAN8 promotes invasion and migration in NPC cell lines *in vitro*. When TSPAN8 is silenced in poorly differentiated CNE2 cells, it leads to the down-regulation of pro-inflammatory factor IL-1β, which inhibits the AKT/MAPK pathway and attenuates metastasis. The authors further explored whether TSPAN8 could predict the prognosis of NPC. Immunohistochemistry experiments indicated that increased TSPAN8 level in NPC was linked to short OS

and metastasis-free survival, suggesting that TSPAN8 could be utilized as a prognostic biomarker for NPC patients (13). This is the first report to suggest that TSPAN8 plays a critical role in the progression and metastasis of NPC.

The TSPAN8 gene encodes for a cell surface glycoprotein that is a member of the 4-transmembrane protein family. It was originally found to be expressed in several types of cancers but not in most normal tissues (14). Subsequently, it was found to be involved in the progression of pancreatic cancer (15), breast cancer (16), lung cancer (17), melanoma (18,19), gastric cancer (20) and hepatocellular cancer (21). It was also discovered that β-catenin stabilization is a molecular response after the onset of TSPAN8 activation in melanoma, that suggests that β-catenin and TSPAN8 are part of a positive feedback loop and sustains a high TSPAN8 expression level (19). The knockout of TSPAN8 down-regulates WNT pathway activity, reduces β-catenin expression and subsequent translocation to the nucleus in gastric cancer (22). The effect of TSPAN8 on β-catenin is mediated by the binding to NOTCH2 (22). In addition, TSPAN8 promotes gastric cancer cell growth and metastasis at least partially through the activation of ERK-MAPK pathway (23). Furthermore, it has been shown that TSPAN8 and its regulators control early melanoma invasion. This indicates that TSPAN8 is a promising novel therapeutic target by regulating downstream of the RAF-MEK-ERK signaling pathway (18). However, it is unknown if the function of TSPAN8 in NPC is associated with EBV virus status. This topic remains one of interest given the prevalence of EBV infection in patients with NPC. Notably, the authors of this study have demonstrated that TSPAN8 may play a role in tumor progression and metastasis through AKT/MAPK pathway in NPC, which implicates a new mechanism of TSPAN8 in regulating cancer cells.

Interestingly, the role of TSPAN8 in promoting cancer stemness has been highlighted recently (16,24,25). Cancer stem cells (CSCs) are a small cell population within the tumor microenvironment (TME). Emerging evidence has suggested that CSCs serve as the basis of cancer metastasis, solid tumor progression, and therapeutic resistance. TSPAN8 has been used as a marker of CSCs and was found to promote cancer stemness through regulating stemness genes: NANOG, OCT4, and ALDHA1 (16,24). It is also an important exosome component to mediate crosstalk between CSCs and their neighboring cells (25). Furthermore, the expression of TSPAN8 is upregulated in breast CSCs and enhances stemness maintenance through the activation of Hedgehog signaling (16). Therefore, it is suggested that TSPAN8 is a potential therapeutic target to overcome treatment resistance contributed by CSCs. It remains undecided that TSPAN8 contributes to distant metastasis and treatment failure in NPC by functioning as CSC stemness guide. It would be worthy to further explore this in order to develop effective therapeutic target to control distant metastasis.

Collectively, this study has shown that TSPAN8 promotes NPC progression and metastasis through AKT/MAPK pathway. TSPAN8 is a potential biomarker for predicting metastasis and prognosis of NPC patients, as well as a therapeutic target for NPC treatment.

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Footnotes

Conflicts of Interest: The authors have no conflicts of interest to declare.

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