OVOL2 links stemness and metastasis via fine-tuning epithelial-mesenchymal transition in nasopharyngeal carcinoma

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Abstract

Rationale: Metastasis is the leading cause of disease-related death among patients with nasopharyngeal carcinoma (NPC). Mounting evidence suggest that epithelial-mesenchymal transition (EMT) is crucial for cancer cells to acquire metastatic ability. In this study, we aim to clarify the extent to which EMT is involved in various cancer properties and identify novel markers for predicting the prognosis of NPC patients.

Methods: Two cellular models derived from the same NPC cell line with distinct metastasis ability were used for microarray analysis to identify key transcriptional factors that drive metastasis. Cell migration and invasion were analyzed by wound healing and Transwell analysis. Lung metastasis was determined by tail vein injection assay. Cancer stemness was analyzed using colony formation and xenograft assay. The EMT extent was evaluated using immunoblotting, RT-qPCR and immunofluorescence of EMT markers. The value of OVOL2 in prognosis was determined by immunohistochemistry in NPC biopsies.

Results: OVOL2 was the most significantly down-regulated EMT transcription factor (EMT-TF) in cellular models of NPC metastasis. Low levels of OVOL2 were associated with poor overall survival of NPC patients and the reduced expression is partly due to promoter methylation and epithelial dedifferentiation. Knockout of OVOL2 in epithelial-like NPC cells partially activates EMT program and significantly promotes cancer stemness and metastatic phenotypes. Conversely, ectopically expression of OVOL2 in mesenchymal-like cells leads to a partial transition to an epithelial phenotype and reduced malignancy. Reversing EMT by depleting ZEB1, a major target of OVOL2, does not eliminate the stemness advantage of OVOL2-deficient cells but does reduce their invasion capacity. A comparison of subpopulations at different stages of EMT revealed that the extent of EMT is positively correlated with metastasis and drug resistance; however, only the intermediate EMT state is associated with cancer stemness.

Conclusion: Distinct from other canonical EMT-TFs, OVOL2 only exhibits modest effect on EMT but has a strong impact on both metastasis and tumorigenesis. Therefore, OVOL2 could serve as a prognostic indicator for cancer patients.

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