KITENIN Enhances Invasion and Metastasis in FOM Cancer Model

Joon Kyoo Lee¹, MD, PhD, Sang Chul Lim¹, MD, PhD, Hee Dae Kim¹, MD, Tae Mi Yoon¹, MD, Jong Hee Nam³, MD, PhD, Hyung Seok Kim², MD, PhD, Min-Ho Shin², MD, PhD, Kyung Keun Kim², MD, PhD

Department of Otolaryngology-Head and Neck Surgery¹, Medical Research Center for Gene Regulation², Pathology³, Forensic Medicine⁴, Preventive Medicine⁵, Chonnam National University Medical School and Hospital, 8 Hak-dong, Dong-gu, Gwangju, Korea

BACKGROUND

KAI1 is a metastatic suppressor gene. The expression of KAI1 in cancer cells results in reduced cell motility and invasiveness. A cDNA clone of VANGL1, a member of the tetraspanin protein family that specifically interacts with the COOH-terminal cytoplasm domain of KAI1, was isolated and renamed KITENIN (KAI1 COOH-terminal interacting tetraspanin). KITENIN is reported to promote metastasis in a mouse colon cancer model.

The purpose of this study was to investigate tumor invasiveness and early lung metastasis by KITENIN in murine floor of mouth cancer models.

MATERIALS AND METHODS

The cDNA of KITENIN and the vector only were transfected into the SCC VII (mouse squamous cell carcinoma line) cells. The transfections were performed using the FuGENE 6 transfection reagent.

The suspension of 5 x 10⁵ cells viable KITENIN- or vector-transfected SCC VII cells were injected into the floor of mouth of C3H/HeJ syngeneic mice deep to the myofibroblastic muscle via an intra-oral approach.

From the 1st week to 6th week after injection, tumor, lung, liver, and brain tissues were obtained from mice each group every week and were evaluated under the light microscope.

RESULTS

For all groups, the tumor invaded the superficial musculature of the floor of the mouth, the deep musculature of the floor of the mouth, the salivary glands, perineural tissue, bone, and skin sequentially.

Fig 1 Pathology of the submental tumor after one week in both groups. There was tumor invasion only in the superficial part of the floor of the mouth musculature (arrow) in the vector group (A, H & E stain, ×40). However, invasion was observed in the deeper part of the floor of the mouth musculature (arrow) in the KITENIN group (B, H & E stain, ×100).

Enhanced invasion into the musculature of the floor of the mouth in KITENIN group.

Fig 2 Salivary gland invasion in the two groups. There was no salivary gland invasion (arrow) in the vector group (A, H & E stain, ×40). However, salivary gland invasion was noted during the first week (arrow) in the KITENIN group (B, H & E stain, ×40).

Earlier and more aggressive tumor invasion into salivary glands in KITENIN group.

Fig 3 Perineural invasion in both groups. There was invasion to the muscular and salivary gland but no perineural invasion (arrows) during the third week in the vector group (A, H & E stain, ×40). However, perineural invasion was noted (arrow) from the second week in the KITENIN group (B, H & E stain, ×200).

Earlier and more aggressive tumor invasion into bones in KITENIN group.

Fig 4 Bone invasion in both groups. There was no bone invasion during the third week in the vector group (A, H & E stain, ×100). However, in the KITENIN group bone invasion was observed (arrows) during the third week (B, H & E stain, ×100).

Earlier skin invasion in KITENIN group.

Fig 5 Skin invasion in both groups. There were muscular and bony invasions but no dermal invasion (arrow) during the fourth week in the vector group (A, H & E stain, ×40). However, dermal invasion was noted (arrow) from the second week in the KITENIN group (B, H & E stain, ×40).

More extensive lung metastasis in KITENIN group.

Fig 6 Pulmonary metastasis during the second week in both groups. Multiple small nodular metastases were observed (arrows) in the vector group (A, H & E stain, ×20). More extensive lung metastasis with vascular invasion (arrows) was demonstrated in the KITENIN group (B, H & E stain, ×40).

CONCLUSION

KITENIN enhanced tumor invasion and lung metastasis in a murine model of squamous carcinoma of the floor of the mouth. An antisense KITENIN strategy might inhibit distant metastasis and progression of head and neck squamous cell carcinoma in human patients.