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MRE11 Promotes Tumor Growth, Metastasis, Resistance to Radiation and Leads to Poor Patient Survival through Akt, CXCR4 and FOXA2 Signaling in Oral Cancer

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MRE11 maintains DNA integrity, DNA replication and telomere length through DNA double-strand breaks repair activity. The aim of this study was to investigate the role of MRE11 in human oral cancer in clinical, in vitro and in vivo settings. Associations of MRE11 expression with clinicopathological characteristics and patient survival were assessed by Cox regression models and Kaplan-Meier analyses. Effects of MRE11 overexpression and knockdown on cell proliferation, migration, invasion, and radioresistance were assessed using oral cancer cell lines (HSC-3, OECM-1, Ca9-22 and CAL-27). Zebrafish xenograft model and nude mouse tail vein-lung metastasis model were employed for investigation of cancer metastasis. Of the 182 oral cancer tissue samples examined, higher MRE11 expression was significantly associated with malignant cancer behavior in oral cancer patients, including tumor size, cancer stage and lymph node metastasis. Furthermore, high MRE11 expression predicted a poor patient survival as well as resistance to radiotherapy. MRE11 overexpression in oral cancer cells significantly promoted cell proliferation/invasion/migration and radioresistance via enhanced DNA repair activity, while MRE11 knockdown had the opposite effect. We also demonstrated that CXCR4, Akt, and FOXA2 were involved in MRE11-promoted cell migration. In conclusion, MRE11 promotes cancer cell metastasis and predicts treatment resistance and poor survival in oral cancer patients. MRE11 and its downstream signaling pathway may serve as targets for therapeutic intervention against oral cancer.

Key words: MRE11, oral cancer, metastasis, DNA repair, survival