ABSTRACT

Angiotensin II type I receptor modulates the migratory and invasive abilities of oral squamous cell carcinoma (OSCC) via MCP-1 signaling

Chun-Chieh Yu a, Chang-Han Chen a,b

a Center for Translational Research in Biomedical Sciences, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung Taiwan
b Department of Otolaryngology, Kaohsiung Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Kaohsiung, Taiwan

Background: Oral squamous cell carcinoma (OSCC) is associated with high rates of recurrence and mortality. Although several well-known markers correlated with poor metastasis/prognosis in OSCC patients was reported, the molecular mechanisms of OSCC development are still not clear. Here, we explored angiotensin II type I receptor (AT1R) and its-elicited signaling pathway participates in the metastatic progression of OSCC.

Materials and Methods: The semi-quantitative-RT-PCR, Q-RT-PCR, western blot, and IHC approaches were used to evaluate the mRNA/protein expressions of AT1R in paired OSCC specimens. Immunohistochemical (IHC) staining of AT1R expression with clinic-pathologic characteristics was examined using univariate and multivariate analyses. Human oral cancer cell lines with overexpressing-AT1R or AT1R-mediated siRNAs were generated by transfection. Transwell chamber, wound healing, western blot, pharmacological inhibitors, and immunohistochemical assays were done to evaluate the signaling pathways that were involved.

Results: We created a bioinformatics scheme consisting of integrating two gene expression profile datasets, including un-pairwise OSCC, and secondary metastatic tumors vs. benign tumors. Among the novel targets identified, AT1R was up-regulated in OSCC tissues and was associated with cancer metastasis. Furthermore, we employed two co-expression strategies to identify in which pathway AT1R was involved. By semi-quantitative-RT-PCR, Q-RT-PCR, Western blot and IHC approaches, we found that AT1R was not only an indicator of poor survival, but also exhibits positive correlations with MCP-1 expression in OSCC specimens. In vitro study, AT1R-overexpressing transfecants could increase the motility of cells via up-regulation MCP-1 expression. Conversely, the motility of oral cancer cells could be suppressed by knock-down endogenous AT1R. These data indicated that AT1R promotes oral cancer metastasis via MCP-1 pathway.

Conclusions: These finding suggested that AT1R is not only an important prognostic factor but also a new therapeutic target in the MCP-1 pathway for OSCC treatment.