Extended Abstract | Research & Reviews: Medical and Clinical Oncology | 2018 | Vol.2 No.2

CGRP Promotes the Migration and Invasion of Human Tongue Squamous Cell Carcinoma Cells through Activation of JNK Signaling Pathway

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Objective: More and more evidence indicates that neurogenesis in cancer is a common phenomenon, which draws our attention to the role of substances released by nerve endings in the development of cancer. Previous studies have shown that neuropeptides influence the migration of prostate cancer cell lines. Mitogen-activated protein kinases (MAPKs) are involved in the migration / invasion of cancer cells. Thus, the present study investigated the effects of the peptide linked to the calcitonin gene (CGRP) on the migration and invasion of squamous cell carcinoma of the tongue (SCC) and the potential role of MAPK signaling pathways. Methods: The effects of CGRP on the migration and invasion of SCC cells from the human tongue (TSCCA cell line) were detected by the Transwell test. The effects of CGRP on phosphorylated expression of MAPKs, including signal signal extracellular kinase (ERK), p38, and N-terminal c-Jun kinase (JNK) from TSCCA cells, were examined using Western Blot. The effects of ERK, p38 and JNK inhibitors on CGRP-induced migration and invasion of TSCCA cells were examined using the Transwell test, the incidence and mortality of which are increasing trends every year around the world [1,2]. Oral squamous cell carcinoma (SCC) is one of the most common types of cancers of the oral cavity, which includes the lips, cheeks, palate, gums and salivary glands, etc. It is still a fatal and disabling disease due to tumor invasion, facial destruction and cervical lymph node metastasis [3]. It is well known that invasion and metastasis are essential characteristics of cancer cells. Recently, some studies have shown that the dose of neurogenesis occurs in several cancers as well as in angiogenesis [4-6]. It is interesting to note that neurogenesis plays an important role in the development of multiple cancers. Neurotransmitters, neuropeptides or synaptic molecules released by nerve endings have a significant influence on tumor migration and invasion, even distant metastases. The calcitonin gene related peptide (CGRP) is a neuropeptide containing 37 amino acid residues discovered in 1982, which is widely distributed in the central nervous system and peripheral organs, including the head, and is known to be associated pain sensation, cardiovascular regulation and vasodilation. Nagakawa et al. has shown that CGRP can promote the invasive potentials of prostate cancer cells by increasing cell motility in vitro. Suzuki et al. reported that serum CGRP levels in patients with prostate cancer are positively correlated with tumor grade and staging. Toda et al. has shown that CGRP fights angiogenesis and tumor growth. The accumulation of evidence has shown that the proliferation, migration and invasion of tumor cells are closely linked to the signaling pathways of protein kinases activated by mitogens. The involvement of MAPK signaling pathways in the progression of oral cancer has been explored. However, the effects of CGRP on the migration and invasion of oral SCC cells have not been reported. Thus, this study was to study the direct effects of CGRP on the migration and invasion of oral SCC cells (TSCCA cell line) by the Transwell test and to explore the potential role of MAPK signaling pathways in cell migration and invasion TSCCA through the CGRP.

The migration of TSCCA cells was determined using a Transwell chamber with a polycarbonate filter (pores of 8 μm, Millipore, USA). For the invasion test, 60 μl of diluted Matrigel (1: 8, Becton Dickinson and Company, USA) was applied to the upper face of the filters. TSCCA cells (3 x 105 cells / ml for migration and 1.5 x 106 cells / ml for invasion) were seeded on the upper chamber in 200 μl of serum-free medium. To examine the effects of CGRP on migration and cell invasion, 100 nM of CGRP (dissolved in 0.1% of DMSO, Sigma, USA) were added in 500 μl of medium containing 10% of FBS in the lower chamber . DMSO (0.1%) was given as a control. To examine the effects of MAPK inhibitors (10 μM, dissolved in 1% DMSO, Tocris Bioscience, UK) for signal-regulated extracellular kinase (ERK), p38 and N-terminal c-jun kinase (JNK) mediated by CGRP and invasion of TSCCA cells, ERK inhibitor PD98059, p38 inhibitor SB203580 or JNK inhibitor SP600125 was added to the upper chamber and CGRP 10

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This work is partly presented at 15th Asia Pacific Oncologists Annual Meeting, September 05-06, 2018 Tokyo, Japan