

# Chemokine Receptors as Biomarkers in Head and Neck Squamous Cell Carcinoma

Head and neck squamous cell carcinoma (HNSCC) is reported to be the 6th most common solid tumor diagnosed in the world [1]. Around 95% head and neck cancers are squamous cell carcinomas originating in the upper aerodigestive epithelial cells [2]. Despite continuous research efforts and progresses in diagnostic and therapeutic strategies, the mortality rates have not significantly changed over the past several decades [3]. Moreover, the five-year survival rate of HNSCC after diagnosis is considerably lower than that of other cancers, such as cervix, colorectal and breast cancer [4,5]. The reason for the limited five-year survival rate of HNSCC could be advanced disease stages, failure in early diagnosis and low efficiency of therapeutic strategies [6,7]. The death of HNSCC is mainly caused by invasion along with regional and/or distant metastatic spreading of tumor cells from primary tumor lesions [8]. Therefore, the key point of the treatment of head and neck cancers is early diagnosis.

So far, numerous genes related to tumorigenesis and tumor progression have been identified and characterized. Some of them, such as *c-myc*, *Ras*, *P53*, *P63*, *cyclin D1* etc., are expressed abnormally in head and neck cancers [3,9-11]. Moreover, other aberrantly expressed proteins have also been found in head and neck carcinoma lesions, including *PTEN* [12,13], *p27* [3,14], *p21* [15] as well as annexins [16], which play significantly roles in the progression, malignancy and prognosis in head and neck carcinoma. These discoveries are helpful in early diagnosis of HNSCC.

Meanwhile, the importance of chemokines and their cognate receptors in head and neck cancers is being revealed by increasing amount of studies. Recently, the expression of CXC chemokine receptor 2 (CXCR2) was reported substantially higher than that in paraneoplastic tissue in laryngeal squamous cell carcinoma [17]. The authors also found that the elevated expression was significantly related with lymph node metastasis, histological grade, and 5-year survival [17]. They concluded that CXCR2 expression could be considered as a potent prognostic marker for laryngeal squamous cell carcinoma patients [17].

Several studies have also documented the significance of CXCR4 in HNSCC tumor progression and organ-specific metastasis [18,19]. Wang et al investigated the expression of CXCR4 in nasopharyngeal carcinoma tissues, and they found that CXCR4 expression was elevated in tumor tissues and the increased expression was correlated with metastatic rates in patients as well as poor overall survival [20]. This finding was consistent with another study which reported that CXCR4 mRNA was significantly higher in HNSCC tissues than in paraneoplastic tissues and its expression were associated with lymph node metastasis and distant metastasis [21]. These findings clearly demonstrate that CXCR4 could also be used to predict prognosis and metastasis in HNSCC patients.

Chen et al. reported that a 64I mutation of the CC chemokine receptor-2 (CCR2) is significantly associated with oral cancer



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susceptibility [22]. Also, another group demonstrated that mutation of MCP-1 gene, which encodes CCR2 ligands, increased the expression of MCP-1 resulting in elevated CCR2 activity which could increase the risk for developing oral squamous carcinoma [23]. The authors predicted that MCP-1 and CCR2 could be used as genetic markers for diagnosis of oral carcinoma squamous [23].

Another CC chemokine receptor, i.e., CCR7, which plays a critical role in the migration of activated dendritic cells to regional lymph nodes, was also found elevated in HNSCC tumor tissues compared with paraneoplastic tissues and the elevated expression of CCR7 was correlated with lymph metastasis and tumor tissue differentiation status [21]. Another study evaluated the expression of CCR7 in primary and metastatic tumor cell lines and biopsies from both primary and metastatic lesions, and it was found that CCR7 expression was elevated in metastatic cells and tissues [24]. These findings reveal an important role of CCR7 in mediating the metastasis and tumor malignancy in HNSCC patients.

Taken together, accumulating evidence indicates that the altered expressions of various chemokine receptors (and their cognate ligands as well) in HNSCC are associated with different cellular events including cell survival, tumor progression, and metastasis. The expression of chemokine receptors is associated with tumor cell differentiation and prognosis of HNSCC patients. Moreover, their expression is also, to some degree, histologically specific, i.e., the expression of these chemokine receptors indicates it is the squamous cell carcinoma rather than other types (such as adenoid cystic carcinoma) [25]. These features, along with other tumor biomarkers, may help oncologists to assess their patients more thoroughly.

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