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Recurrence and cancer-specific survival according to the expression of IL-4Rα and IL-13Rα1 in patients with oral cavity cancer

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Abstract ***Background:*** Interleukin-4 (IL-4) and interleukin-13 (IL-13) are anti-inflammatory and immunomodulatory cytokines that play crucial roles in cancer progression. However, the clinical significance of the expression of these cytokines and their receptors (IL-4R) in oral cavity squamous cell carcinoma (OSCC) is unknown. Therefore, we evaluated the expression of IL-4R in OSCC specimens by immunohistochemistry (IHC) and analysed its relationship to recurrence and survival.

Methods: A total of 186 patients with OSCC were enrolled, and the expression of IL-4Rα and IL-13Rα1 on their primary tumour specimens was evaluated by IHC and correlated to clinicopathologic parameters, recurrence and survival.

Findings: High expression of IL-4Rα and IL-13Rα1 was observed in 60 (32.3%) and 165 (88.7%) patients, respectively. IL-4Rα expression was inversely correlated with parameters reflecting primary tumour burden, including tumour size, tumour stage and depth of invasion at the initial diagnosis ($P < 0.05$). High expression of IL-4Rα also correlated with a greater risk of recurrence ($P = 0.002$), but was unrelated to cancer-specific survival (CSS,

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$P = 0.118$). Conversely, high IL-13Rα1 expression correlated with reduced recurrence ($P < 0.001$) and increased CSS ($P < 0.001$) in OSCC patients.
Interpretations: High expression of IL-4Rα correlated with increased recurrence, while high IL-13Rα1 expression had an inverse relationship to recurrence and CSS in OSCC patients.

1. Introduction

Chronic inflammation plays a vital role in carcinogenesis. In the tumour microenvironment, the balance between tumour-associated proinflammatory activity and anti-tumour immunity can determine whether cancer cells continue to proliferate or undergo apoptosis. The inflammatory state of the tumour is influenced by cytokines released by peritumoural immune cells, tumour cells and other types of tumour-associated host cells, such as endothelial cells and fibroblasts [1]. In the oral cavity, inflammatory reactions take place continuously in response to microorganisms and foreign materials, and the inflammatory state of the oral cavity may drive the progression of oral cavity cancers (OCC). Therefore, an analysis of the peritumoural inflammatory environment in OCC may enhance our understanding of OCC tumour biology and lead to new treatment options.

Interleukin-4 (IL-4) is an anti-inflammatory and immunomodulatory cytokine produced mainly by activated T cells that shares many biologic activities with interleukin-13 (IL-13) [2]. The IL-4 and IL-13 receptors have four different subunits, and various functional units are generated by combinations of the subunits. The type I IL-4 receptor (IL-4R) is composed of the common γ-chain and IL-4Rα, and it is present on lymphoid T and natural killer cells, basophils and mast cells. The type II IL-4R is the result of heterodimerisation of IL-4Rα with IL-13 receptor α1 (IL-13Rα1), and it is found on non-lymphoid cells and tumour cells [3,4]. Therefore, the expression of both IL-4Rα and IL-13Rα1 must be determined in order to distinguish the type II IL-4R from the type I IL-4R on various cells within the tumour microenvironment.

There have been many reports that IL-4, IL-13 and their receptors are associated with progression in various types of carcinomas [5,6]. IL-4 acts as an autocrine survival factor through Stat6 signalling and upregulation of survivin, resulting in resistance to death ligand-induced apoptosis [7,8]. IL-13 also operates via the Stat6 pathway, by binding to the type II IL-4R, and promotes cancer cell survival [9]. In the field of head and neck cancer (HNC), most studies have focused on the plasma levels of inflammatory cytokines, and the impact of IL-4R and its ligands on cancer progression has not been reported [10–12]. Therefore, studies on the relationship between IL-4R and OCC progression may suggest a promising target for the treatment of OCC.

In this study, we aimed to characterise the expression of IL-4R on OCC specimens by immunohistochemical staining (IHC) and to evaluate its correlation with clinicopathologic parameters and patient survival. The expression of IL-13Rα1 was also evaluated to differentiate the type I IL-4R on tumour-infiltrating immune cells from the type I IL-4R on non-immune cells, and to validate the results of the IL-4R analyses.

2. Patients and methods

2.1. Patients

Between 2000 and 2011, a total of 253 patients diagnosed with oral cavity squamous cell carcinoma who underwent curative surgery at our tertiary referral centre were preliminarily analysed. Seventy-seven patients were excluded because of a history of prior therapy, palliative treatment for initially detected distant metastasis, inadequate clinical follow-up data or a lack of sufficient specimen to use for tissue microarray (TMA). Therefore, 186 patients were included in the final analysis. This study was reviewed and approved by the Institutional Review Board of our institute and the requirement for informed consent from each patient was waived.

2.2. Treatments

All patients underwent radical resection of the primary tumour with combined neck dissection. Patients without clinical nodal metastasis underwent selective neck dissection (ND) involving levels I–III or I–IV. Patients with clinical nodal metastasis underwent modified radical or radical ND including levels I–V, and bilateral ND was done if primary tumours involved the midline and contralateral neck metastases were suspected. Patients with advanced-stage tumours or with adverse pathologic features were treated with postoperative radiotherapy (RT) or chemoradiotherapy (CRT).

2.3. Follow-up

After the initial resection, patients were regularly followed by clinical examination and imaging. They were scheduled for clinic visits every 1–2 months during the