行政院國家科學委員會專題研究計劃成果報告

鼻咽癌組織中 IL-10 及 Fas-L 的表現（2/2）

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Fas-L expression in nasopharyngeal carcinomas

Abstract:

Nasopharyngeal carcinoma (NPC) is an epithelial cancer with a high incidence in South-east Asia. How it escapes attack of host immune system is not fully understood. Recently, pieces of evidence show that Fas-ligand (Fas-L)-mediated apoptosis may involve in immune privilege of tumours. We analyzed the expression of Fas-L by immunohistochemical methods from NPC specimens prior to radiation therapy. Eighty cases of NPC were studied in groups according to clinical staging (UICC system), these included 14 cases of stage I, 35 cases of stage II, 12 cases of stage III, and 19 cases of stage IV. Forty-two of the 80 cases (52.5%) showed positive Fas-L expression including 0 of the 14 (0%) stage I NPC, 20 of the 35 (57.1%) stage II NPC, 7 of the 12 (58.3%) stage III NPC, and 15 of the 19 (78.9%) stage IV NPC (p<0.05). Eleven of the 27 (40.7%) T1, 20 of the 36 (55.6%) T2, 4 of the 6 (66.7%) T3, and 8 of the 11 (72.7%) T4 showed positive Fas-L expression (p=0.288). Thirteen of the 36 (36.1%) N0, 18 of the 30 (60%) N2, 7 of the 9 (77.8%) N3, and 4 of the 5 (80%) N4 showed positive Fas-L expression (p<0.05). Seven of the 8 (87.5%) M1, and 35 of the 72 (48.6%) M0 showed positive Fas-L expression (p=0.059). These findings show that the expression of Fas-L in NPC probably related to degree of staging especially in nodal status.

Key words: nasopharyngeal carcinoma, Fas-ligand
Introduction:

Nasopharyngeal carcinoma (NPC) is one of the most common types of epithelial cancer in South-east Asia including Taiwan (1). The histopathologic picture of NPC is characterized by a marked lymphocytic infiltration mainly composed of T cells (2). Although some of infiltrated T cells bear activation antigens indicating the manifestation of local immune reaction (3,4), they fail obviously to suppress the growth of tumour cells. Several inhibitory factors, such as prostaglandins (5), gangliosides (6) and TGF-β (7) produced by tumour cells were suspected to play roles in the tumour-mediated immunosuppression. Nevertheless, none of them were effective enough to inactivate irreversibly the T cell function.

Recently, there are pieces of evidence showing that Fas-L may contribute to the immune privilege of tumours other than those processes achieved by inhibitory immune factors or physical barriers. For instances, hepatocellular carcinomas not only escape Fas-mediated killing by down regulation of the expression of Fas molecules but also have the ability of active destruction of T-lymphocytes by expressing Fas-L on tumour cells (8). Melanoma cells express also Fas-L on cell surface. Injection of Fas-L-bearing mouse melanoma cells in mice led to rapid tumour formation. In contrast, tumourigenesis was delayed in Fas-deficient lpr mutant mice in which immune effector cells cannot be killed through the ligation with Fas-L (9). Based on those findings, we speculated that Fas-L may also participate in tumourigenesis of NPC and analyzed therefore the expression of Fas-L gene in NPC tumour.

Materials and Methods

Patients

The present work comprised 80 previously untreated primary NPC patients. According to the 1997 UICC staging system, 14 patients belonged to stage I, 35 patients belonged to stage II, 12 patients belonged to stage III, and 19 patients belonged to stage IV. These included 27 cases of T1, 36 cases of T2, 6 cases of T3, and 11 cases of T4. Lymphadenopathy was presented in 44 patients. Thirty patients had N1, 9 had N2, and 5 with N3. Eight patients presented with distant metastasis.

Immunohistochemistry

Nasopharyngeal biopsy specimens obtained before treatment were fixed in 10% formalin and processed for routine histological examination in paraffin wax. The localization of Fas-L was detected by immunostaining using an IgG anti-Fas-L polyclonal antibody (N-20, Santa Cruz Biotechnology, CA). This antibody recognizes
the intracellular N-terminus region of human. Cryosection of NPC tumour samples were transferred onto glass slide coated with poly-L-lysine. Cells were fixed with 4% formaldehyde in phosphate buffered saline (PBS), permeabilized with 0.1% Triton-X-100 in PBS at room temperature for 15 min and subsequently incubated in 0.5% bovine serum albumin for 2 hr. Reaction was performed with anti-Fas-L antibody for 3 hr followed by a goat anti-rabbit IgG conjugated with horseradish peroxidase (Dako, CA). The immune complexes were made visible by 3-amino-9-ethylcarbazole (Zymed, CA) then stained counter with HE-staining. After extensive washing with PBS, cells were mounted in a drop of p-phenylenediamine/glycerol, examined under a microscopy and photographed.

**Results**

Forty-two of the 80 cases (52.5%) showed positive Fas-L expression including 0 of the 14 (0%) stage I NPC, 20 of the 35 (57.1%) stage II NPC, 7 of the 12 (58.3%) stage III NPC, and 15 of the 19 (78.9%) stage IV NPC (p<0.05). Eleven of the 27 (40.7%) T1, 20 of the 36 (55.6%) T2, 4 of the 6 (66.7%) T3, and 8 of the 11 (72.7%) T4 showed positive Fas-L expression (p=0.288). Thirteen of the 36 (36.1%) N0, 18 of the 30 (60%) N2, 7 of the 9 (77.8%) N3, and 4 of the 5 (80%) N4 showed positive Fas-L expression (p<0.05). Seven of the 8 (87.5%) distant metastatic cases, and 35 of the 72 (48.6%) non-metastatic patients showed positive Fas-L expression (p=0.059).

**Discussion**

Several questions arise as to the mechanism of induction and functional significance of Fas-L on NPC tumour. Up-regulation of Fas-L expression can be found in activated lymphocytes, which is important in down-regulation of immune responses (9,10). Infection with HIV may also up-regulate Fas-L as demonstrated by the finding that soluble and membrane-bound forms of Fas-L were produced in greater amounts in peripheral blood mononuclear cells obtained from HIV-1-infected persons than from normal controls (11). On the other hands, constitutive Fas-L expression is observed in several non-lymphoid tissue including the lung, liver, small intestine, prostate and uterus (12). To our knowledge, epithelial cells do not express Fas-L. As yet, how the expression of Fas-L is stimulated during neoplastic transformation of these nasopharyngeal epithelial cells is not well elucidated. In this study, we show that the expression of Fas-L in NPC probably related to degree of staging especially in nodal status.
References


