

SOLUBLE INTERLEUKIN-2 RECEPTOR IN CANCER

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1. ABSTRACT

Levels of serum sIL-2R (soluble interleukin-2 receptor) reflect the total amount of activated T lymphocytes in tumor infiltrating lymphocytes of cancer tissues and metastatic organs, because a part of α -chain of IL-2R is released into the bloodstream on the attachment of IL-2 (interleukin-2) to its specific IL-2R membrane. In most malignant diseases, elevated levels of serum sIL-2R are found, compare to normal control. Serum sIL-2R is a useful parameter for evaluating the disease stage and monitoring the disease progression during the post-treatment follow-up, though it is not an organ-specific parameter.

2. INTRODUCTION

Interleukin-2 (IL-2), which is a glycoprotein with molecular weight 15,500 daltons, 133 amino acid residues long, plays a pivotal role for the generation and regulation of the immune response (1). A large number of research on IL-2 contributed to the biological characterization of this important cytokine. IL-2 serves to activate many key cells in the immune system, especially in T-lymphocytes. Moreover, anti-tumor activity of IL-2 had been studied in experimental and clinical studies. IL-2 is binding to its specific membrane receptor (interleukin-2 receptor (IL-2R)) by autocrine and/or paracrine (2). The IL-2/IL-2R system is focused by many investigators (3-5), because of

its importance and clinical applications in immunological status in cancer-bearing patients.

3. BIOLOGY OF IL-2R AND sIL-2R

Three components of IL-2R have been identified: α , β , and γ chain. α chain is specific for IL-2, and also is known as Tac antigen or CD25. α chain of IL-2R is a 55kDa glycoprotein with an extracellular domain of 219 amino acid residues, a transmembrane domain of 19 residues, and a cytoplasmic domain of only 13 residues (6). Its intracellular dominant is too short to act as a consensus sequence for signal transduction (6, 7). In a manner similar to other peptide hormones, IL-2 acts through binding to specific plasma membrane receptors (IL-2R) on newly synthesized T lymphocytes. A part of α chain of IL-2R is released from its affinity membrane receptor and detected as a form as soluble IL-2R (sIL-2R) in the bloodstream (Figure1). α chain is specific for IL-2, whereas β chain, a 75 kDa glycoprotein, is shared between IL-2 and IL-15, and γ chain, a 64 kDa glycoprotein, is known as common γ chain shared by IL-2, IL-4, IL-9, and IL-15 (8). Thus, α chain is conceivable to a key to receptor specificity for IL-2. Meanwhile, β and γ chain have an important role to act as intracellular signalling through the Janus throsine kinase family (JAK) (9). JAK 1 is

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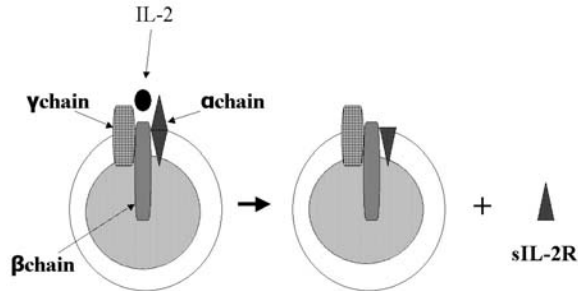


Figure 1. Production of soluble IL-2R (sIL-2R): IL-2 combines to its specific receptor in an autocrine and/or paracrine manners. The α -chain of IL-2R is separated from its receptor and is released into the peripheral blood stream as serum soluble IL-2R.

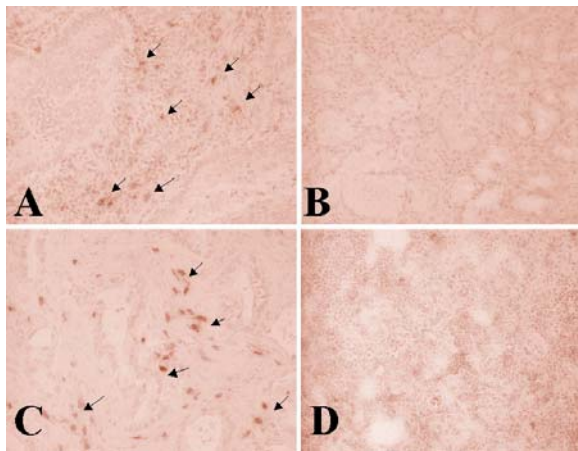


Figure 2. Immunohistochemical staining of IL-2R: **A** Gastric cancer tissues; many IL-2R-positive cells (arrows) were recognized in the interstitium. **B** Normal gastric tissues; there were no IL-2R-positive cells. **C** Metastatic lymph node; many IL-2R-positive cells (arrows) were found, similar to the gastric cancer tissues. **D** Normal lymph node; there were no IL-2R-positive cells.

constitutively bound to β chain and JAK 3 is bound to γ chain with high affinity after cellular activation (6, 7).

4. MECHANISM OF INCREASED LEVELS OF SERUM sIL-2R IN CANCER PATIENTS

Humoral mediators, produced by cancer cells, have stimulated mainly T lymphocytes, resulting in the production of IL-2. This IL-2 is bound to IL-2R by autocrine and/or paracrine, and T lymphocyte is activated to proliferate and generate the immune response. The measurement of IL-2 itself in the serum is difficult and unstable because of its very short half-life span (about 3 minutes (8)). Therefore, the serum sIL-2R, thanks to its relatively long half-life span and easy of detecting it in serum, is popularly favored to measure the quantity of T lymphocytes activated by IL-2. In fact, increased levels of serum sIL-2R have been found in patients with diverse

disease (10), including infectious diseases, autoimmune diseases, and malignant diseases (Table 1).

The clinical significance of sIL-2R in various cancers has been described in detail as following below.

5. sIL-2R IN CANCER OF DIGESTIVE TRACT

5.1. Gastric cancer

Levels of serum sIL-2R in patients with gastric cancer are higher than those of normal control (10-12). There is no association between the histological type and levels of serum sIL-2R (11, 13). On the other hand, levels of serum sIL-2R in patients with lymph node metastasis are higher than those in patients without lymph node metastasis (11, 13, 14). In the immunohistochemical study, the IL-2R-positive cells are found to be uniformly distributed in the interstitium of gastric cancer tissues. On the other hand, the IL-2R-positive cells are not identified in normal gastric tissues. Similarly, the IL-2R-positive cells are identified in the metastatic lymph node, whereas they are not found in the normal lymph nodes (Figure 2). Though the levels of serum sIL-2R are not strictly parallel to existence of the IL-2R-positive cells, its is conceivable that activated T lymphocytes in cancer tissues and metastatic lymph nodes play potent antitumor roles and release a large number of sIL-2R into the bloodstream (14). Furthermore, even in early gastric cancer, levels of serum sIL-2R with lymph node metastasis are high than those without lymph node metastasis. Therefore, serum sIL-2R might be qualified as a predictor of lymph node metastasis in early gastric cancer, when endoscopic mucosal resection or minimally invasive gastrectomy has been chosen for treatment (15). Moreover, serum sIL-2R may predict the outcome of patients with gastric cancer, as it is recognized to be an independent indicator for the prognosis by multivariate analysis (13).

5.2. Colorectal cancer

Levels of serum sIL-2R of Dukes stage C in colorectal cancer have increased, compared with those of normal control and Dukes stage A (16). The higher levels of serum sIL-2R in patients with lymph node metastasis are recognized, compared with those without lymph node metastasis (17). And, markedly elevated levels of serum sIL-2R are found in patients with liver metastasis (18). Preoperative levels of serum sIL-2R thus seem to reflect the stage of the disease in colorectal cancer. Moreover, serum sIL-2R may be a useful predictor of the prognosis (18, 19). In the immunohistochemical staining of IL-2R, the IL-2R positive cells are recognized in colorectal cancer tissues and metastatic lymph nodes. Therefore, levels of serum sIL-2R might reflect the amount of activated T lymphocytes in cancer and metastatic organs. Moreover, a correlation of sIL-2R with immunosuppressive acidic protein (IAP) is recognized in colorectal cancer. IAP has various immunosuppressive effects on a host immune system. It seems to contradictory that there is a relationship between sIL-2R, which reflect the activated immunity, and IAP, which suppresses it. IAP may suppress an overreaction of immunity in the local area with cancer cell and inhibit the hyperactive immune response from spreading that has harmful influences on the host (17).

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Table 1. Levels of serum sIL-2R in various malignant diseases

| Condition | n | sIL-2R (U/ml) (mean \pm SEM) | p value (vs control) |
|-------------------|-----|--------------------------------|----------------------|
| Control | 39 | 276 \pm 19 | - |
| Gastric cancer | 230 | 491 \pm 29 | 0.0029 |
| Colorectal cancer | 155 | 442 \pm 32 | 0.0065 |
| Esophageal cancer | 34 | 490 \pm 46 | 0.0001 |
| Breast cancer | 103 | 470 \pm 37 | 0.0017 |

Data of patients admitted to Department of Surgery, Saitama Medical School. Diverse malignant diseases demonstrate the high levels of serum sIL-2R. n=Number of subjects

5.3. Esophageal cancer

Compared with the healthy control, the patients with esophageal squamous cell carcinoma have higher levels of serum sIL-2R (20, 21). Levels of serum sIL-2R are correlated with lymph node metastasis, tumor size, distant metastasis, disease stage, and prognosis (20, 21). Thus, serum sIL-2R is eligible to be a indicator of the disease progression and prognosis. In the immunohistochemical staining, IL-2R-positive cells is seen not only in infiltrating mononuclear cells but also in the cytoplasm and membrane of the cancer cells (21). And, there is a correlation between levels serum sIL-2R and immunohistochemical expression score of IL-2R α (20). Furthermore, the expression of IL-2R α mRNA is identified in cancer cells by in situ hybridization. According to these findings, in addition to activated T lymphocytes, cancer cells may be an important source of elevated levels of serum sIL-2R in patients with esophageal squamous cell carcinoma.

5.4. Pancreatic cancer

Levels of serum sIL-2R in patients with pancreatic cancer is higher than those of normal control or chronic pancreatitis (22). In the patients with distant metastases (liver or peritoneum), levels of serum sIL-2R are not elevated in comparison with healthy control. This may suggest that the immunological response is suppressed in pancreatic cancer patients with distant metastasis or that the patients without IL-2 mediated anti-tumor response develop distant metastasis (22). Patients with low levels of serum sIL-2R live shorter than patients with high levels. This is not in accordance with cancers in other digestive organs (stomach, colorectal, and esophagus)(13, 18, 20). The immunological response via IL-2/IL-2R system in pancreas cancer may differ from other digestive organs.

5.5. Hepatocellular carcinoma

Levels of serum sIL-2R in patients with hepatocellular carcinoma (HCC) infected by chronic hepatitis B and/or C are elevated, compared with healthy control (23). Levels of serum sIL-2R return to normal ranges after surgical treatment. Furthermore, measurements of sIL-2R are more accurate than measurements of alpha feto-protein (AFP) levels in detecting recurrence of disease after surgical treatment of HCC (23). Therefore, sIL-2R is a more sensitive marker of early-stage disease, successful surgical treatment, and recurrence of HCC after surgical treatment. However, sIL-2R measurements can not replace AFP determinations, because levels of sIL-2R have a possibility of an elevation by the progression of viral hepatitis. sIL-2R is considered to be a useful adjunct for screening the patients who are at high risk for developing HCC (23).

6. sIL-2R IN CANCER OF ENDOCRINE AND GYNECOLOGICAL ORGANS

6.1. Breast Cancer

Levels of serum sIL-2R in breast cancer are higher than in normal control (24-26). Level of serum sIL-2R in cases with lymph node metastasis or distant metastasis are elevated, compared with those in cases without these metastasis (25). As there are no relationships between levels of serum sIL-2R and menstruation, estrogen receptor, or progesterone receptor, an influence of female sex hormones to activation of T lymphocytes is conceivable to be very low or nothing at all. Though CA 15-3 is frequently used to monitor the clinical course of the disease in breast cancer, it is not always elevated when the metastasis develops. Thus, measurement of serum sIL-2R may give additional valuable indications of disease progression and response to therapy, especially when CA 15-3 is not elevated (26). In the immunohistochemical study, a large number of IL-2R positive cells are recognized in breast cancer tissues, whereas none in normal breast tissues, as well as gastric cancer (14) and colorectal cancer (16). Moreover, there is a correlation between levels of serum sIL-2R and tumor size in breast cancer (25). This finding differs from those in gastric and colorectal cancer (11, 16). This discrepancy may be explained by a difference between parenchymal organs such the breast and ductal organs such as the stomach, colon and rectum.

6.2 Uterus cancer

Levels of serum sIL-2R in patients with the cervix or endometrial carcinoma of uterus are increased before treatment, compared to normal control. Levels of serum sIL-2R after the decrease of the mass by radiotherapy have been returned to normal range (27). Therefore, the measurement of serum IL-2R might be useful to evaluate the prognosis and the efficacy of treatment for these diseases.

6.3. Ovarian cancer

In patients with ovarian cancer, levels of serum IL-2R are higher than those with benign ovarian tumors (28, 29). Elevated levels of sIL-2R are also detected in ascites of patients with ovarian cancer (30). As levels of sIL-2R in serum and ascites are elevated in patients with advanced ovarian cancer, the measurements of sIL-2R in these samples are qualified to be a potential complementary marker to CA125 for early detection and management of ovarian cancer (30).

6.4. Thyroid cancer

In postoperative patients without metastasis or local recurrence of differentiated thyroid carcinoma, under

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the hypothyroidal status, levels of serum sIL-2R are lower when compared to normal control. The supplement of thyroxine is associated in these cases with an increase up to normal levels of serum sIL-2R (31). This fact suggests that levels of serum sIL-2R appear to be strictly dependent on the thyroidal status. In spite of the hypothyroidal status under the supplement of thyroxine off, high levels of serum sIL-2R are also observed in cases of differentiated thyroid carcinoma with metastasis (31). Therefore, thyroidal status and disease progression is conceivable to modulate sIL-2R.

7. sIL-2R IN HEAD AND NECK CANCER

A relationship between levels of serum sIL-2R and the stages of advanced tumor is observed in patients with head and neck squamous cell carcinoma (32). In Cox multivariate analysis, level of serum sIL-2R is found to be the most predictive factor of survival in these patients (32). Therefore, level of serum sIL-2R at the time of diagnosis represents an independent prognostic variable for predicting the risk of locoregional recurrence and survival for patients with head and neck squamous cell carcinoma (32,33). In patients with metastatic brain tumor from lung cancer, levels of serum sIL-2R in those with regional lymph node metastasis show higher than those without lymph node metastasis. Furthermore, patients with the extreme high level levels of serum sIL-2R show poor prognosis (34). High levels of serum sIL-2R are found in glioma patients with poor performance status and also in primary brain lymphoma (34). The IL-2R positive infiltrating lymphocytes are detected in surrounding glioma tissues by the immunohistochemical staining (34). This finding is similar to gastric cancer (14), colorectal cancer (17), and breast cancer (25).

8. sIL-2R IN LUNG CANCER

In both adenocarcinoma and squamous cell carcinoma of lung, levels of serum IL-2R are higher in advanced stages than in early stages. On the other hand, in small cell carcinoma of lung, levels of serum IL-2R are within normal range, even though they are in advanced-stage disease (35). Therefore, level of serum sIL-2R increases in association with both the disease stage and the histological type in lung cancer (35). And, the persistence of increased levels of serum sIL-2R is associated with a higher early relapse rate in patients with operable non-small cell lung cancer (36). Therefore, the measurement of serum sIL-2R in the perioperative period would present a prognostic factor in operable non-small cell lung cancer (36). Furthermore, the increased levels of serum sIL-2R are observed in patients surviving only in short terms and in those who do not response to chemotherapy (37). Based on these data, the measurement of serum sIL-2R is beneficial in prognostic evaluation and in the clinical surveillance of patients with advanced lung cancer submitted to chemotherapy (37). As the elevated preoperative levels of serum sIL-2R in non-small cell lung cancer reflect the occurrence of intrapulmonary metastasis, it is also useful in the detection of the intrapulmonary metastasis preoperatively (38).

9. sIL-2R IN LEUKEMIA AND MALIGNANT LYMPHOMA

Elevated levels of serum sIL-2R can be detected during the blastic phase of chronic myelogenous leukemia (2). Conversely, the increased levels of serum sIL-2R can not be found in stable chronic myelogenous leukemia (2). In acute lymphoblastic leukemia, levels of serum sIL-2R are also higher than normal control (39). Moreover, higher levels of serum sIL-2R are associated with a poorer treatment outcome (39). On the other hand, elevated levels of serum sIL-2R can not be detected in patients with multiple myeloma (2). Levels of serum sIL-2R are elevated in both T-cell and B-cell lymphoma (2). The measurement of serum sIL-2R has a clinical value in predicting treatment outcome and overall survival in patients with Hodgkin and non-Hodgkin lymphoma (2, 40). Furthermore, serum sIL-2R is a useful predictor of relapse in malignant lymphoma, as well as serum thymidine kinase (TK) that reflect either the tumor burden or the tumor proliferation rate (41).

10. sIL-2R IN MALIGNANT MELANOMA

Levels of serum sIL-2R in patients with melanoma are higher than in normal control, and the extreme increased levels are recognized in those that develop metastasis during follow-up, which suggest that the sIL-2R is linked to metastatic progression in malignant melanoma (42). And, the sIL-2R is a good indicator for predicting occult metastasis in selected cases with malignant melanoma (43). As levels of serum sIL-2R are correlated the disease progression, it is a useful clinical parameter in evaluating the disease stage and monitoring disease evolution in malignant melanoma (44).

11. sIL-2R IN RENAL CELL CANCER AND CARCINOMA OF THE URINARY BLADDER

The elevated levels of serum sIL-2R are found in patients with renal cell carcinoma, compared to normal control (45). And, the disease-free patients with renal cell carcinoma have lower values of serum sIL-2R than those with recurrent active disease (46). Therefore, as well as other solid tumors, the serum sIL-2R may have a clinical significance in monitoring the disease progression.

12. THE FUTURE OF sIL-2R IN CLINICAL APPLICATIONS

12.1. Clinical significance as a tumor marker

As described above, serum sIL-2R is a valuable predictor for the disease stage and the recurrence of diverse malignant diseases, though it is not an organ-specific parameter. Especially, serum sIL-2R is able to predict the lymph node metastasis in some malignant diseases (15, 17, 20), probably because activated T lymphocytes stimulated by cancer cells metastasized to lymph nodes release a large amount of sIL-2R into the bloodstream (15). However, a prudent and cautious investigation must be performed in determining the occurrence of lymph node metastasis, as the increased levels of serum sIL-2R is also found in some infectious and autoimmune diseases.

12.2. Therapy targeting the interleukin-2 receptor

In some malignancies, such as HTLV-1 induced adult T cell leukemia/lymphoma, hairy B-cell leukemia, Hodgkin's disease and cutaneous T-cell lymphoma, the expression of α subunit of IL-2R is recognized on their cellular surface (7). It is supposed that the IL-2-mediated growth of the malignant cells is interrupted by anti-IL-2R antibody and thereby apoptotic cell death occurs by deprivation of IL-2. Therefore, on selective these disease, using specific anti-IL-2 α receptor antibody has been going to perform in clinical applications. In the clinical trial against adult T-cell leukemia by Waldmann et al, anti-IL-2R antibody induced the anti-tumor effects in some cases (47). In hematological malignancies, these trials are recently conducted (48, 49) and the efficacy of the monoclonal anti-IL-2 receptor antibodies is going to be investigated.

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