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INVITED REVIEW

On the Role of sIL-2R Measurements in Rheumatoid Arthritis and Cancers

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A soluble IL-2 receptor (sIL-2R) is a circulating form of a membrane receptor localized on lymphoid and some cancer cells. The biological function of sIL-2R has not been completely understood. Substantially, it seems to reflect T-lymphocyte activation in diseases of different pathology. Moreover, the soluble receptor has been considered, at least in part, responsible for unsuccessful immunotherapy with IL-2 in cancers. Several lines of evidence indicate sIL-2R measurements to be useful in determining disease progress and prognosis. This review summarizes current knowledge on the sIL-2R behavior in RA and solid cancers of varied etiology.

INTRODUCTION

In 1984 Rubin and coworkers [1] reported the presence of soluble IL-2 receptors in cultured human T-cell leukemia virus I (HTLV I)-positive T lymphocytes and peripheral blood mononuclear cells (PBMCs) stimulated with mitogens. Ever since then, a number of research surveys have been conducted to gain a better understanding of the substance and the functions that sIL-2Rs play in the immune system. Twenty years after the report of the Rubin's group, the biological function of sIL-2R has not yet been completely understood, though it is regarded a marker of T-cell activation [1]. Significantly, taking into consideration its high (as compared to IL-2) serum concentration, sIL-2R measurements in serum/plasma give a better tool for the assessment of the immune system activity.

STRUCTURE AND FEATURES

Soluble IL-2R is part of a membrane receptor for interleukin-2, which can be localized on the cell surface of different lymphoid cell lines including activated T and NK cells, monocytes, eosinophils [2, 3, 4], and on some tumor cells [5, 6, 7]. IL-2R ectodomains are thought to be proteolytically cleaved from the cell surface [8, 9, 10] and not produced as a result of posttranscriptional splicing [11]. This membrane receptor is important for cell stimulation with interleukin-2 (IL-2), which is one of the most significant interleukins in the immune system. IL-2R exists in three different forms: alpha (IL-2Rα, CD25, previously Tac antigen, M = 55 kd), beta (IL-2Rβ, CD122, M = 75 kd), and gamma chains (IL-2Rγ, CD132, M = 64 kd). A model of an IL-2 receptor is shown in Figure 1.

Being shared with other cytokine receptors, beta and gamma chains belong to a cytokine receptor superfamily [12], also called a hematopoietin receptor family [13]. The beta subunit is common to IL-15 receptor [14], and the gamma chain (known also as "common gamma chain," γ_c) to IL-4, IL-7, IL-9, and IL-15 receptors [14, 15, 16, 17]. Soluble IL-2Rβ can be found in the supernatants of stimulated peripheral blood lymphocytes [18] and during inflammatory diseases in the serum [19], whereas sIL-2Rγ can be found in the serum [20] and in synovial fluid (SF) [21], but not in the PHA-activated human PBL cultures [22].

The IL-2R subunits demonstrate different binding affinities to IL-2, with the highest noted for a structure composed of all the three subunits, in which the alpha chain is required for the receptor clustering and IL-2 signal transduction [23]. Beta and gamma subunits show intermediate affinities, while the alpha chain alone shows the lowest and is not capable of signal transmitting into cells [24]. This latter structure is not normally present on the resting cells. Cellular expression of the alpha receptor followed by its release into the circulation takes place upon lymphocyte stimulation.

Structurally, the alpha chain is not related to the cytokine receptor family. As a membrane receptor it is a 251-amino-acid-residue polypeptide, which is organized into

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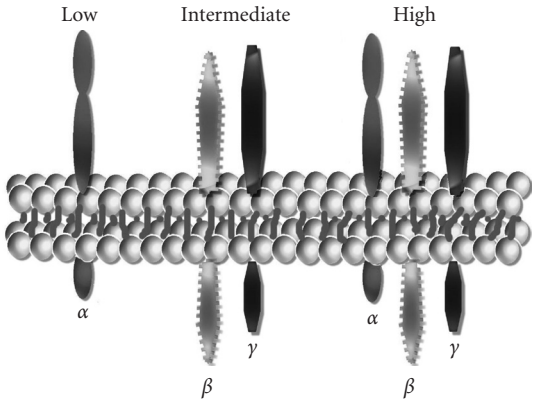

FIGURE 1. IL-2 membrane receptor structures with different affinities for IL-2 binding. Receptor α alone binds IL-2 with low affinities (kd 10^{-8} M), not allowing signal transduction into cells. Receptor $\beta\gamma$ and $\alpha\beta\gamma$ complexes demonstrate intermediate (kd 10^{-9} M) and high (kd 10^{-11} M) affinities, respectively, enabling signal transduction.

two sushi (CCP/SCR) domains linked to each other with a 30-amino-acid chain [25], required for IL-2 binding [26]. The extracellular domains are the largest part of the receptor, which consists of 219 residues, anchored to the cell with a small 19-residual transmembrane domain, and a cytoplasmic domain consisting of 13 amino acids [27]. Therefore, the soluble form that comprises the extracellular part is only about 10 kd lighter than the membrane-bound receptor. Hence, the molecular weight of the soluble receptor has been estimated as 35–40 kd in the case of HTLV I-positive T cells and 45–50 kd for activated PBMC [1].

BIOLOGICAL SIGNIFICANCE

Amongst the three subunits which can be released from the cell surface, sIL-2Rα appears to possess the best diagnostic value in a number of diseases associated with T-cell stimulation. Substantially, membrane receptor expression and release take place after leukocyte stimulation; therefore, the presence of the alpha chain in the circulation is a good measure of T-cell activation. Another advantage is its specificity to only the IL-2 receptor, whilst the beta and gamma chains are shared with other cytokine receptors. Moreover, contrary to gamma-chain levels, considerable amounts of the alpha chain can be found in the serum [22]. The majority of the studies, therefore, focused on sIL-2Rα, which can be measured not only in the serum/plasma [28], but also in other bodily fluids, including synovial fluid, cerebrospinal fluid [29], and urine [28].

One of the most interesting biological features of sIL-2R is its ability to bind IL-2 with an affinity similar to that of the form present on the cell surface [30]. Such findings are suggestive of the immunosuppressive function attributed to this molecule. A proposed mechanism of this interaction is presented in Figure 2. Gooding et al [31] investigated IL-2 bioavailability during immunotherapy with this interleukin, as influenced by the high concentrations of its soluble receptors. They found that the elevated sIL-2R levels may lead to a decreased cellular response to IL-2. Hence sIL-2R determination in plasma/serum may be helpful for qualifying patients to receive IL-2 immunotherapy [31].

When considering the usefulness of sIL-2R for clinical assessment, one must pay attention to its variability caused by several intrinsic factors and keep this in mind during the selection of control groups for clinical trials. Amongst these, one is age dependence [28, 29, 30, 31, 32]. Gotoh et al [28] established that serum and urine sIL-2R concentrations in childhood (age 1–14 years) appear to be 2 times higher than those in adulthood (age 21–67 years). Similar results were obtained by Sack et al [32], who measured serum sIL-2R in a group of 275 children between 3 and 17 years of age. In this study sIL-2R concentration decreased along with the age of the children, but remained higher than in the adults. High in childhood, soluble receptor concentration rises again in adulthood, resulting in a tendency of older people to have higher levels of this protein than young adults [33, 34].

Food intake is also one of the factors that should be taken into consideration when studying sIL-2R levels. Nutrition is of great importance to immunity and normal immune responses. An adequate nutrient supply provides integrity to the immune system. In this context, the dramatic restriction of food intake must be associated with depression of the immune defense. This thesis had been investigated in two studies, which brought forth contradictory results. Nagata et al [35] reported the significant decrease of serum sIL-2R levels in anorexia. Unfortunately this survey was performed on a very small group of anorectic subjects who were underweight or normal. A more extensive study by Allende et al [36], in which anorectic subjects were divided into different groups depending on their nutritional status, did not corroborate these findings. Although several immunological parameters were distorted in underweight patients, the sIL-2R concentration did not differ from that of the controls. This somewhat limited evidence, and the discrepancies between the studies, shows that more attention should be focused on the sIL-2R concentration as influenced by the nutritional status, especially in the cancer anorexia/cachexia syndrome.

Other factors, including time of day or night, nocturnal sleep and nocturnal wakefulness, do not alter serum sIL-2R concentration [37].

AUTOIMMUNE DISEASES AND CANCERS

Autoimmune diseases and cancers were found to be associated with an impairment in the T-cell-mediated immunity [38], and IL-2 and its membrane receptor were established to be crucial to this process [39, 40]. At present,

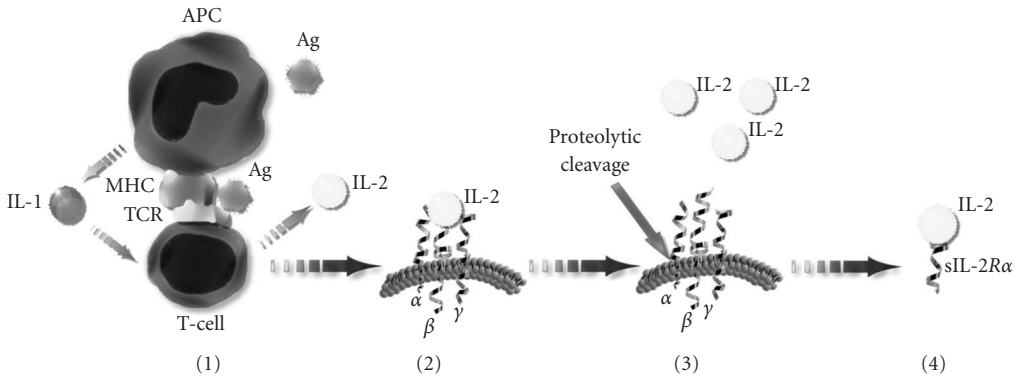

Figure 2. Immunosuppressive function of sIL-2R. (1) An internalized antigen is presented by MHC on APC to TCR. In response to stimulation with the antigen, activated T cells produce IL-2 and express IL-2α receptor on their surface. (2) IL-2 binds to $\alpha\beta\gamma$-complex receptor on the surface of lymphocyte. This interaction induces signal transduction into cell and proliferation. (3) Proteolytic cleavage of the IL-2Rα chain from the cell membrane. IL-2 can be bound to the remaining units of intermediate affinities. (4) Soluble IL-2R binds IL-2, preventing its interaction with membrane receptor.

IL-2 is not only thought of as a T-cell growth factor, but also as a factor of immune self-tolerance [41].

Autoimmunization is a process that comprises of intensified production of the proinflammatory IL-1, IL-6, and TNF-α, and a decrease in the level of anti-inflammatory IL-2. IL-6 is known for its ability to suppress T-cell responses. In addition to this, elevated sIL-2R levels are at least in part responsible for the depression of the IL-2-dependent immunity.

Table 1 summarizes results of the clinical trials which aimed to establish serum sIL-2R concentrations in RA and cancers. This data provides information on the sIL-2R utility for cancer staging.

Rheumatoid arthritis

Rheumatoid arthritis (RA) is an inflammatory disease leading to joint destruction. The molecular mechanism of synovitis is associated with T-cell activation and an elevated production of proinflammatory cytokines, metalloproteinases, and adhesion molecules. In human studies, an increase of sIL-2R levels during this process has been noted, both in serum/plasma and in synovial fluid (SF) [8, 42, 43, 44]. It was established that high levels of sIL-2R found in SF are produced by mononuclear cells [45]. Cultured PBMCs from RA subjects release considerable amounts of sIL-2R spontaneously. No correlation, however, can be seen between the membrane receptor expression and its release [46].

Detailed clinical trials show that serum sIL-2R levels are related to disease duration [44] and a decline in sIL-2R concentration may result from joint improvement [47]. Interestingly, Klimiuk et al [48] established that serum sIL-2R concentration is related to a histological pattern of synovitis. Earlier studies failed to establish any correlation between these two variables [44].

Some reports indicate relationships between sIL-2R and laboratory markers of inflammation, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) [44, 45, 46, 47, 48]. These findings were not confirmed by Fröde et al [49]. Other studies found positive correlations between sIL-2R in serum and IL-1beta in SF [50] or erythropoietin in serum [51], and negative correlations for serum haemoglobin [51] or 1,25-dihydroxyvitamin D_3 [52], which is a known suppressor of activated T cells.

Findings from clinical trials raise a question on whether sIL-2R concentration in serum provides a reliable immunological marker to assess disease activity in RA. Earlier studies reported the possible advantages of sIL-2R measurements for these purposes [53]. Tebib et al [44] do, however, question the utility of sIL-2R as such a marker, since it is not specific nor sensitive to measure disease activity in an outpatient RA population. It also does not correlate with disease activity after pharmaceutical treatments with gold salts, methotrexate, or sulfasalazine [54, 55, 56]. Mangge et al [57], however, point to sIL-2R determination as relevant in monitoring juvenile RA, because it allows the ability to ascertain disease activity in cases in which common inflammatory parameters are unaltered. Suenaga et al [58] suggest sIL-2R measurements to be helpful for the early diagnosis of RA in patients with joint pain, but without symptoms of bone or joint destruction.

Cancers

Cancer growth and development is associated with stimulation of the immune system, including enhanced IL-2R expression in immune cells and its shedding into the circulation. Numerous studies have attempted to establish connections among clinical symptoms of neoplasm, markers of inflammation, and sIL-2R levels in body fluids. These reports documented the usefulness of sIL-2R for monitoring anticancer therapy, in both chemotherapy and surgical treatment [59].

Malignant cells of human lymphoid tumors are thought to be the major source of serum sIL-2R. Wasik et al [60] demonstrated in an animal study that the sIL-2R

Table 1. Serum IL-2Rα concentrations in cancers and autoimmune diseases. Numbers in round brackets are numbers of study participants. ng means not given.

Disease	sIL-2R in controls	sIL-2R in disease	Disease/control ratio	Reference
Breast cancer	428 pg/mL (11)	Stages I, II: 1426 pg/mL (20)	3.3	[76]
	428 pg/mL (11)	Stages III, IV: 1184 pg/mL (10)	2.8	[76]
Renal-cell carcinoma	291 U/mL (10)	Stage II: 596 U/mL (27)	2	[85]
	291 U/mL (10)	Stage III: 776 U/mL (8)	2.7	[85]
	291 U/mL (10)	Stage IV: 1310 U/mL (17)	4.5	[85]
Esophageal squamous-cell carcinoma	1020 pg/mL (103)	Stage I: 1017 pg/mL (11)	1	[86]
	1020 pg/mL (103)	Stage II: 1384 pg/mL (30)	1.4	[86]
	1020 pg/mL (103)	Stage III: 1309 pg/mL (44)	1.3	[86]
	1020 pg/mL (103)	Stage IV: 1721 pg/mL (36)	1.7	[86]
Head and neck cancer	1036 pg/mL (22)	1496 pg/mL (19)	1.4	[65]
Nasopharyngeal carcinoma	1050 pg/mL (32)	Stage I: 1356 pg/mL (17)	1.3	[64]
	1050 pg/mL (32)	Stage II: 1932 pg/mL (23)	1.8	[64]
	1050 pg/mL (32)	Stage III: 2416 pg/mL (36)	2.3	[64]
	1050 pg/mL (32)	Stage IV: 2903 pg/mL (37)	2.8	[64]
Lung cancer	821 U/mL (22)	Stages IIIa-b: 880 U/mL (21)	1.1	[73]
	821 U/mL (22)	Stage IV: 1149 U/mL (18)	1.4	[73]
	507 U/mL (30)	Stages IIIb, IV: 906 U/mL (76)	1.8	[70]
Adenocarcinoma of lungs	54 pM (18)	Stages I, II: 47 pM (17)	0.9	[69]
	54 pM (18)	Stage IIIa: 71 pM (11)	1.3	[69]
	54 pM (18)	Stage IIIb: 87 pM (10)	1.6	[69]
	54 pM (18)	Stage IV: 110 pM (18)	2	[69]
Squamous-cell lung carcinoma	54 pM (18)	Stages I, II: 73 pM (9)	1.4	[69]
	54 pM (18)	Stage IIIa: 186 pM (9)	3.4	[69]
	54 pM (18)	Stage IIIb: 126 pM (9)	2.3	[69]
	54 pM (18)	Stage IV: 86 pM (5)	1.6	[69]
Nonsmall-cell lung carcinoma	355 U/mL (21)	Stage Ia: 372 U/mL (26)	1	[71]
	355 U/mL (21)	Stage Ib: 409 U/mL (11)	1.2	[71]
	355 U/mL (21)	Stage IIa: 425 U/mL (3)	1.2	[71]
	355 U/mL (21)	Stage IIb: 391 U/mL (5)	1.1	[71]
	355 U/mL (21)	Stage IIIa: 420 U/mL (10)	1.2	[71]
	355 U/mL (21)	Stages IIIb, IV: 614 U/mL (10)	1.7	[71]
Ovarian cancer	58 pM (20)	Stages IIIb, IV: 701 pM (30)	12.1	[79]
Pancreatic cancer	648 U/mL (43)	Stage I: 1185 U/mL (16)	1.8	[82]
	648 U/mL (43)	Stages II, III: 1039 U/mL (60)	1.6	[82]
	648 U/mL (43)	Stage IV: 649 U/mL (25)	1	[82]
Colorectal cancer	347 U/mL (33)	Stage I: 364 U/mL (26)	1	[87]
	347 U/mL (33)	Stage II: 349 U/mL (45)	1	[87]
	347 U/mL (33)	Stage IIIa: 467 U/mL (26)	1.3	[87]
	347 U/mL (33)	Stage IIIb: 350 U/mL (11)	1	[87]
	347 U/mL (33)	Stage IV: 644 U/mL (34)	1.9	[87]
	413 U/mL (98)	Stage I: 515 U/mL (8)	1.2	[87]
	413 U/mL (98)	Stage II: 456 U/mL (9)	1.1	[87]
	413 U/mL (98)	Stage III: 412 U/mL (13)	1	[87]
	413 U/mL (98)	Stage IV: 821 U/mL (8)	2	[87]
Rheumatoid arthritis	355 U/mL (34)	567 U/mL (32)	1.6	[88]
	366 U/mL (12)	687 U/mL (ng)	1.9	[89]

Table 1. Continued.

Disease	sIL-2R in controls	sIL-2R in disease	Disease/control ratio	Reference
Vasculitis	258 pg/mL (8)	Active 1279 pg/mL (19)	5	[90]
	258 pg/mL (8)	Inactive 739 pg/mL (19)	2.9	[90]
Systemic sclerosis	34 pM/mL (15)	112 pM/mL (42)	3.3	[91]
	68 pmol/L (11)	85 pmol/L (13)	1.3	[92]
Scleroderma	1757 pg/mL (12)	Initial stage: 1606 pg/mL (7)	1	[93]
	1757 pg/mL (12)	Advanced stage: 3466 pg/mL (16)	2	[93]

production depended on the tumor size. Several studies proved, however, that not only the lymphoid cancer cells express IL-2 receptors on their surface, but also that some nonlymphoid cancer cells do, including pulmonary carcinomas and melanoma [5, 6, 7]. Other nonlymphoid tumors, however, such as prostatic or ovarian carcinoma, and glioblastoma multiforme, do not seem to be the source of sIL-2R [60].

Melanoma

Melanoma cells are capable of expressing IL-2 receptors on their surface [5], and sIL-2R has been found to correlate with disease progression [61]. In metastatic melanoma, sIL-2R seems to reflect tumor burden [62]. Contrary to these findings, other researchers did not see any connection between these two variables [63]. Elevated serum sIL-2R concentration in advanced cutaneous melanoma can provide information about worsened patient status and chances of survival [62].

Head and neck cancers

Similarly to other neoplasms, sIL-2R levels in head and neck cancers tend to be elevated [64, 65]. Lai et al [66] established that an increase in serum sIL-2R concentration in nasopharyngeal carcinoma correlates with clinical staging. In other studies, high serum concentrations at time of diagnosis were highly correlated with shorter survival [67]. On the other hand, low levels of the soluble receptor point to a reduced chance of metastasis development by cancer patients within a 3-year period. Tartour et al [67] postulated that serum sIL-2R can be employed in head and neck cancers as an independent prognostic marker of distant metastases development and as a marker of the patient's survival.

One of the advantages attributed to sIL-2R measurement is its response to therapy. A study by Lai et al [66] established that regular sIL-2R serum measurement in about 90% of patients having sIL-2R levels elevated at diagnosis provided prognostic data to estimate the immune response to radiotherapy.

In the late nineties of the last century (1990s), Chinese researchers investigated the advantages of photodynamic therapy (PDT) in nasopharyngeal carcinoma and its effect on the serum IL-2R and IL-2 concentrations and *NK* cell activity [68]. PDT procedure included laser superficial gasification of tumor lesions and the administration of a photosensitive agent followed by photoirradiation. The post-PDT levels of sIL-2R were found to be significantly lower, but IL-2 levels were significantly higher than those before the therapy. Also, a markedly increase in *NK* cell activity was noted as a result of therapy.

Lung cancer

Yano et al [7] discovered that tumor cells in pulmonary adenocarcinoma are capable of expressing IL-2R and releasing it into circulation. In another study they also found that the receptor concentrations in adenocarcinoma and squamous-cell carcinoma were higher in the advanced than in the early stages [69]. In the more advanced stages of small-cell carcinoma, however, sIL-2R concentration remained unchanged.

Aleman et al [70] found high sIL-2R and other proinflammatory cytokine concentrations as being predictive of shorter survival among patients with advanced lung cancers, while others gave the evidence that sIL-2R measurements can be useful for metastases detection in non-small-cell lung carcinoma [71]. They showed that elevated presurgical sIL-2R levels were indicative, with a sensitivity of about 90%, of intrapulmonary metastases [71].

Some other practical roles attributed to sIL-2R measurement are its utility in prediction of early recurrences after tumor resection [72], as well as indication of shorter survival in nonoperable patients treated with chemotherapy [73].

Breast cancer

Patients with breast cancer tend to have elevated serum sIL-2R concentrations [74, 75, 76]. No association with the disease stage, however, has been found [74]. An increase in serum sIL-2R levels was observed in metastatic cancers when compared to nonmetastatic tumors [77]. Sharma et al [75] reported the possible immunomodulatory effect of the IL-2 soluble receptor which suppressed infiltration of blood lymphocytes into the tumor tissue.

Sabbioni et al [78] noted that sIL-2R concentration in the early breast cancer stages can be influenced by the type of surgery performed. These researchers found that women, who had undergone a total mastectomy, had lower sIL-2R concentrations than those having conserving surgery. In opposition to surgical operations, chemotherapy does not seem to influence serum sIL-2R levels [76].

Ovarian cancer

In advanced epithelial ovarian cancer, high serum IL-2R levels have been found to correlate with an impairment of T-cell response [79]. Moreover, sIL-2R in serum and ascitic fluid tends to be higher in advanced epithelial ovarian cancer than in the serum and peritoneal fluid of healthy women [80]. No correlation was found, however, between sIL-2R levels in these two bodily fluids [80].

Renal-cell carcinoma

Renal-cell carcinoma (RCC) is associated with sIL-2R elevation in plasma, which gradually increases with the clinical stages [31]. It has been established that RCC subjects, having an elevated sIL-2R concentration, had a shorter rate of survival than those with a lower concentration [31]. German researchers found that the membrane-bound IL-2 receptor expression in patients who received a perioperative pretreatment with IL-2 is accompanied by sIL-2R release [81]. This finding may explain why IL-2 immunotherapy could be unsuccessful in many cases of RCC.

Pancreatic cancer

No associations between serum IL-2R concentration and tumor grading, or lymph node involvement, resectability, sex, and local tumor invasion in pancreatic adenocarcinoma were observed [82]. Interestingly, Gansauge et al [82] noted a trend toward lower sIL-2R concentration in patients with distant metastases, which is in opposition to other studies, in which positive trends or correlations have been described in various metastatic cancers [62, 77, 83]. These researchers also found higher sIL-2R levels in patients who are positive to anti-p53 autoantibodies. An earlier study established that the anti-p53 autoantibodies-positive pancreatic cancer patients are significantly less metastatic than those who are anti-p53 autoantibodies negative [84].

Colorectal cancer

According to Saito et al [83] colorectal cancer patients who are liver metastasis positive, tend to have higher serum sIL-2R concentrations than those without metastases. Moreover, receptor concentration was found to be independent of the presence of lymph node metastases and not associated with the histopathological background [83].

CONCLUSIONS

Several lines of evidence indicate sIL-2R as a nonspecific marker of T-cell activation in diseases including RA and various cancers. Therefore its application for cancer staging seems to be rather questionable. A number of surveys, however, support the utility of sIL-2R measurements in monitoring disease progression and dynamics, and early detection of recurrent disease. Moreover, by reflecting immune response during anticancer therapy, it offers a tool for selecting an appropriate treatment strategy and enables evaluation of its effectiveness.

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