Cancer Immunol Immunother (2004) 53: 262–274
DOI 10.1007/s00262-003-0469-5

REVIEW

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Tumour escape: antitumour effectors too much of a good thing?

Received: 12 September 2003 / Accepted: 24 October 2003 / Published online: 18 December 2003

Abstract Although even "spontaneous" tumours are immunogenic and are commonly infiltrated by tumour antigen-specific T cells (at least in melanoma), most tumours are not completely rejected by the host, and cancer progresses. There is a growing realisation that many responses defined as antitumour effector mechanisms act as double-edged swords and under different conditions either become ineffective or even protumorigenic. Examples are interleukin 2 (also proapoptotic for activated T cells), interferon γ (by induction of ligands for T and NK cell inhibitory receptors), angiogenesis inhibition (by hypoxia-mediated induction of growth factors promoting metastasis), and macrophage free radical-mediated cytotoxicity (by inhibiting T cells). Immune selection pressure itself, resulting in outgrowth of resistant tumour variants could also be viewed in this light. On the other hand, knowledge of the many tumour escape pathways offers the theoretical possibility of reconstituting antitumour immunity. Tumour escape from immunosurveillance represents the last series of hurdles to be overcome in formulating truly effective cancer immunotherapy, but given the immense plasticity of the tumour cell, and the complex balance between pro- and antitumour activity of the very same effector pathways, this remains a major challenge.

Keywords Tumour antigen · Immunosurveillance · Tumour rejection · T cell–mediated immunity · Escape

This article is based on presentations made at the first Cancer Immunology and Immunotherapy Summer School, 8–13 September 2003, Ionian Village, Bartholomeio, Peloponnese, Greece.

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Introduction

The recent renaissance of interest in the idea of immunosurveillance against tumours has arisen as a result of new data requiring reexamination of the reasons for rejecting this theory over the past couple of decades [38]. The evidence against immunosurveillance was derived largely from an inability to detect remarkable differences in cancer occurrence in athymic nude mice compared to their normal wild-type equivalents [146] and because cancer incidence in long-term immunosuppressed organ transplant recipients was thought either not to be increased or to be limited to cancers with a viral etiology. However, athymic mice are not completely devoid of functional T cells [66], and with longer follow-up, a larger range of cancers does appear at increased frequency in transplant recipients [49, 82]. Increasing awareness of the latter among transplant physicians is leading to routinisation of specialist cancer screening follow-up in such programs (for recent examples, see [7, 155, 170]).

For many years now, clinical vaccination trials have sought to trigger or enhance antitumour immunity, but always with rather disappointing results. Many explanations (apart from the nonexistence of anticancer immunity) could account for the unimpressive success rates, from the classical concept of immunoselective pressure giving rise to resistant variants, to the more recent realisation that tumour-induced alterations to the patients' immune system may subvert anticancer responses. These mechanisms may be classified into the following major groups:

1) alteration of MHC class I and tumour antigen expression
2) dysregulated expression of adhesion / accessory molecules by tumour and/or antigen-presenting cells
3) secretion of immunosuppressive soluble factors either by tumour cells or infiltrating T cells or both
4) induction of immune nonresponsiveness via anergy induction or clonal deletion of responding T cells
5) induction of suppressor cells

6) changes in T-cell signal transduction molecules
7) tumour utilisation of products of stimulated leukocytes, i.e. immunostimulation of cancer.

The following sections provide brief examples of some key findings that have contributed to our current understanding in each of these categories and, where appropriate, directions to recent reviews on these topics, as well as indications for remediation.

Alteration of MHC and tumour-antigen expression

MHC class I–restricted cytolytic T cells (CTLs) are thought to be major effectors of anticancer immunity. Loss of HLA antigens from tumour cells would therefore prevent their recognition and lysis by such CTLs. There is a lot of data documenting that down-regulation of HLA-A and HLA-B alleles is common and clinically important [47, 76], with reduced levels of class I expression predicting clinical outcome [69]. Even total loss of HLA expression is not uncommon [16]. Several mechanisms are responsible, but total loss of class I expression is usually a result of deletion of β2-microglobulin [108]. Another common reason for decreased class I expression is loss of peptide transporter function, usually regulatory rather than deletional and therefore susceptible to remedial manipulation, e.g. with cytokines, as shown for TAP-1 [136]. Down-regulation of MHC antigen by tumour cells is a powerful strategy to avoid killing by MHC-restricted CTLs; accordingly, poor prognosis has been reported to result from HLA loss [4]. However, tumours lacking MHC class I expression might be expected to become more susceptible to immunotherapy based on NK cells. This phenomenon may underlie reports inconsistent with the above paradigm which suggest that HLA loss may sometimes predict better not worse survival [94], or even the extreme example of uveal melanoma where high HLA expression is seen and correlates with metastatic spread and poor prognosis [67].

In addition to down-regulation of "classical" HLA antigens, tumour cells may up-regulate expression of MHC molecules such as HLA-E, which ligate inhibitory receptors such as CD94/NKG2A that are expressed both by NK cells and CTLs. The expression of these NKIR is up-regulated by cytokines such as IL-15 and TGF-β, both of which can be produced by tumour cells [9, 54]. Moreover, even cytokines such as IFN-γ may act as double-edged swords via up-regulation of NKIR ligands on tumour cells via up-regulation of HLA-G [89]. Consistent with this, there is also a correlation between higher serum levels of soluble HLA-G in melanoma patients and advanced stage of disease and tumour load [154]. For recent reviews on the role of NKIR, see [20, 26].

Loss of tumour-antigen expression may not occur infrequently compared with the loss of the HLA molecule presenting tumour peptide, but it has been difficult to document. Experiments in mice have shown that immunoselection against dominant tumour antigens often but not always results in reduced MHC class I expression [36]. Powerful circumstantial evidence for similar phenomena in humans derive from an extensive clinical study examining 532 melanoma lesions from 204 patients after vaccination with gp100 peptide. The frequency of lesions highly expressing gp100 significantly decreased after therapy whereas the expression of MART-1 was essentially unchanged [126]. HLA loss cannot strictly be excluded but would require that gp100 production was reduced by HLA loss, which is unlikely. More recently, a range of mutations in the PA-1 target antigen in mice in the absence of MHC loss has been documented as a major mechanism accounting for tumour escape after adoptive immunotherapy [8].

The emergence of tumour variants under selective pressure of a specific immune response reflects the usual acquisition of therapy resistance resulting in loss of susceptibility to therapy. A common approach to alleviate this is to increase the dose of therapeutic agent. This may be more feasible for adoptive immunotherapy than chemotherapy and stem cell transplantation. Indeed, in some models, increasing the number of effector cells can destroy tumour cells before they have time to evolve resistant variants [91] – here is therapy as a race against time. In this context, either in vivo, or in in vitro propagation of large numbers of T cells for use in adoptive immunotherapy, a further problem arises: cell senescence caused by extensive replication of somatic cells (for reviews, see [39, 112]).

Expression of adhesion or costimulatory molecules by tumour and/or dendritic cells

Tumour-antigen presentation by dendritic cells in the context of appropriate costimulation is critical for eliciting CTLs, and accessory molecule expression by tumour cells is important in their susceptibility to such CTLs. Both DC and tumour cell adhesion/accessory/costimulatory molecule expression is dysregulated in cancer and contributes materially to tumour escape. Early work showed that tumour-infiltrating DCs were strongly MHC class II^+ but failed to express the important costimulatory molecules CD80 or CD86 (thereby inducing T-cell anergy), whereas DCs in inflammatory infiltrates such as in Crohn's disease lesions were highly functional and all $CD80/86^+$ [23]. Failed attempts to normalise DC function in cancer have included treatment with Flt3-ligand [40], and use of neutralising antisera against IL-10, VEGF, TGF-β or PGE_2 [72]. In other model systems in which DCs progressively lost MHC class II expression, Flt3L treatment also proved ineffective at restoring DC integrity [27].

Effector cells, once generated, must interact with their target cells, initially via antigen nonspecific adhesive mechanisms. Tumour cells of different histologies frequently show relatively decreased levels of important

adhesion molecules, such as ICAM-1 [158], which may have functional consequences [45]. IFN-γ treatment can up-regulate ICAM-1 on colon carcinoma cells and increase their lytic susceptibility [12]. Cancer cells may also lack expression of other important costimulatory molecules, such as CD40 [62], the absence of which on epidermal tumours has been suggested to facilitate escape [156]. Von Leoprechting et al. reported that advanced stages were $CD40^-$ whereas primary tumours and even metastases were $CD40^+$ [157]. Moreover, CD40 ligation on melanoma cells enhanced their susceptibility to lysis by Melan-A/MART-1–specific CTLs, so loss of CD40 expression would prevent this and contribute to escape [157]. CD40 expression may be associated with a more favourable prognosis in some other tumours as well, e.g. diffuse large B-cell lymphoma [83].

As with NKIR mentioned above, costimulatory family receptor/ligand pairs are also present not only as positive but also as negative regulatory effectors. Recent awareness of the widespread expression of ligands such as PD-1L on several different types of cancer and the negative effects that they mediate on antitumour T cells [34] may make these molecules critical targets for immunoregulation therapy. Again, care must be exercised here; commonly employed immunomodulatory cytokines such as IFN-γ increase the level of PD-1L expression [34]. Undoubtedly, yet more negative receptors remain to be discovered [160]; complete knowledge of all such possible interactions might be beneficial in manipulating responses in the desired direction.

Secretion of immunosuppressive substances

It has been known for many years that sera of cancer patients can contain an impressive variety of immunosuppressive proteins, ranging from acute phase reactants with nonspecific inhibitory properties, to adhesion molecules blocking cell interactions or apoptosis. Reactivity not only to tumour but also to nontumour antigens may be depressed in cancer patients and contribute to their increased susceptibility to infection. Soluble forms of adhesion molecules such as CD54, CD58, and others may correlate with disease progression, as has been suggested for plasma sCD54 levels [53, 132]. Gangliosides may be inhibitory at the level of antigen-presenting cell function [113, 138]. Serum levels of soluble Fas may also contribute to tumour escape [13, 68, 153]. Molecules commonly overexpressed in tumour cells, such as MUC-1 and MUC-2, may also be immunosuppressive for T cells in soluble form [73] and associate with poor survival and poor anticancer responses in patients on immunotherapy [87]. Annexin II, overexpressed in several tumours, may also inhibit T-cell proliferation [1]. The human neutrophil proteins known as ''defensins'' may also fall into this category [59]. Tumours can also exert nonspecific suppressive activity, e.g. by secreting adenosine as a result of their hypoxic metabolism. Adenosine can inhibit IL-12 and stimulate IL-10 production by monocytes, contributing to these suppressive effects [84]. Another simple substance possibly functioning in this way may be tryptophan, secreted by tumour-associated macrophages (for review, see [93]).

Many cytokines secreted by either tumour, immune system or both, can exert immunosuppressive effects. The best known of these are probably TGF-β and IL-10, but a whole range of others, including those most commonly thought of as immunostimulatory, may also have this effect. IL-10 has been shown to hinder a number of immune functions, i.e. T-lymphocyte proliferation, T_H1-type cytokine production, antigen presentation, and lymphokine-activated killer cell cytotoxicity. Elevated levels of IL-10 concentrations have been found in patients with various solid tumours, as well as haematological malignancies [41, 133] and may have prognostic significance in a variety of cancers [31]. Many negative effects of IL-10 on the host immune system have been described, including inhibition of proinflammatory cytokines, and down-regulation of both the initiation and effector phase of inflammatory and delayed-type hypersensitivity responses in vivo (for review, see [96]). Kim et al. [73] described secretion of IL-10 by carcinoma cells and showed that intralesional treatment with IFN-α induced tumour regression, associated with down-regulation of IL-10 mRNA. We have shown that CML cells spontaneously secrete large amounts of IL-10 ex vivo and that IFN-α acts to decrease this while increasing IL-1β secretion without altering TNF-α [111]. IL-10 might therefore play a central role as one of the mechanisms responsible for immune dysregulation in cancer patients. Taken together, the majority of reports suggests that when tumours or/and tumor-infiltrating lymphocytes (TILs) express higher levels of IL-10 (and TGF-β), this mostly results in deleterious immunosuppressive effects.

There is also evidence that other cytokines, such as circulating IL-6, are associated with worse survival and greater extent of disease [130]. IL-6 production could contribute to peripheral T lymphocyte dysfunction, enabling tumour cells to escape immune surveillance by preventing the antitumour T_H1 immune responses [42]. In lung cancer patients, levels of serum IL-6 are greater even than in patients with chronic obstructive pulmonary disease and acute infection; thus it is unlikely that the increases in IL-6 reflect merely a systemic inflammatory response [35]. In melanoma, patients responding to therapy showed a serum IL-6 level twice that of controls, whereas in nonresponders this factor was 11-fold, suggesting a strong correlation between IL-6 level and clinical status [98]. In breast cancer, patients with more metastases and patients refractory to therapy had higher levels of IL-6 in their serum; they also had poorer survival such that multivariate analysis showed that IL-6 and disease-free interval were the major prognostic factors [172]. On the other hand, the prognostic relevance of single cytokine markers may vary with the type of tumour examined: for example, in hepatocellular

carcinoma, it has been reported that serum IL-10 levels but not serum IL-6 levels predict clinical outcome after resection [22]. It is therefore, and is likely to remain, an extremely difficult task to synthesise available data into a common model. Given this complexity, a unifying hypothesis has great attraction; one such is the rule of thumb that T_H1 predominance equates with host-mediated tumour rejection, but that T_H2 predominance inhibits this process. Although this may end up to be the case more often than not, it is obviously not a universal finding under all circumstances. For example, IL-4–transduced tumour vaccines trigger type 2 polarisation in both CD4 and CD8 cells; the CD8 cells are instrumental in rejecting the tumours, in an IL-4–dependent fashion involving other CD8 cells and probably also NK cells [127]. There is evidence that IL-10 can also enhance tumour rejection [125], elicit cytotoxic immune memory due to the combined action of NK cells, $CD8^+$ T cells and neutrophils [50], and, in conjunction with CD80-CD28 costimulation, can prime tumour-reactive CTLs [166]. This is consistent with the ability of IL-10 to prevent T-cell apoptosis [110, 147]. Nevertheless, particularly for IL-10, many negative effects on the host immune system have been described, including inhibition of proinflammatory cytokine production by macrophages [32], and down-modulation of both the initiation and effector phase of inflammatory and delayed-type hypersensitivity responses in vivo [117]. Moreover, DCs exposed to IL-10 may induce anergy in peptide-specific antitumour CTLs instead of activating them [142]. IL-10–pretreated DCs also tend to prime IL-4–secreting T cells, perhaps by default due to the down-regulation of IL-12 production [85] and lower levels of expression of costimulatory molecules [18]. In addition, IL-10–exposed DCs are more susceptible to lysis by autologous NK cells [18], which would decrease antigen-presenting capability but might also help to prevent anergy induction. Recently the mechanism responsible for the decreased MHC class I presentation in the mouse lymphoma RMA and the mastocytoma P815 was shown to involve a down-regulation of the expression of the TAP-1/2 proteins and of their functions in the IL-10–expressing tumours [129]. An intriguing possibility is therefore that IL-10 might be one of the mechanisms responsible for the finding that TAP-1/2 expression is frequently turned off in human tumours (for review, see [135]), promoting their escape from tumour-specific CTLs, as discussed above. Zeidler et al. [171] confirmed that cellular and viral IL-10 affects antigen presentation and MHC class I expression in EBV-infected human B lymphocytes through its ability to reduce TAP-1 expression. Since not only T_H2 cells but also many tumours themselves produce IL-10, this could contribute to immunosuppressive effects and the class I down-regulation (also class II down-regulation) commonly seen in tumour cells.

Considering the complexity and multitude of effects that IL-10 exerts on the immune system, as reviewed above, it could be asked what the net effect of a systemic overexpression of this cytokine on host antitumour surveillance will be. As transgenic mice expressing IL-10 under the control of the IL-2 promoter were found to be unable to limit the growth of immunogenic tumours [56], this is consistent with the argument made above that a deleterious effect of this cytokine on the host resistance to tumour growth will predominate in vivo. On the other hand, IL-10 has been shown to exert antiangiogenic and antimetastatic effects in certain murine models [64], so that it is remains difficult to dissect out the contradictory activities of this cytokine in tumour immunology.

Inducing immune nonresponsiveness in TILs

T-cell destruction

Perhaps the most direct example of tumour escape by induction of unresponsiveness in T cells is the finding that secreted protein from tumours may be presented in the thymus and cause clonal deletion of newly generated T cells, according to the usual paradigm of central tolerance induction [80]. Another possible tumour escape mechanism involving clonal deletion, but this time peripheral deletion, relies on the fas/fas-ligand pathway. Shortly after activation, T cells begin to express fas (CD95). Some time, but not immediately thereafter, $CD95^+$ T cells acquire susceptibility to fas-mediated cell death. Therefore, under certain conditions remaining to be precisely defined, the interaction of fas-ligand with CD95 can induce T-cell apoptosis but other outcomes are also possible. The nonapoptotic consequences of fas signaling may have been relatively overlooked thus far (for review, see [159]). Many types of tumour have been reported to express fas ligand following the initial publication in 1996 [57] (for review, see [123]), although this is controversial [21]. It was proposed [124] that contrary to the prevailing view that tumour cells cause the death of antitumour T cells by expressing FasL, the FasL is in fact expressed by T lymphocytes upon activation after tumour cell recognition, causing them to kill themselves *(*"suicide"*)* and each other *(*"fratricide"*)* through the same caspase-based mechanism. Some of the disparities in the literature may perhaps be due to variation in tumour stage, within lesions or after selection. For example, in gastric carcinoma it has been argued that fas-ligand positivity of metastatic but not primary tumour is functional, in terms of inducing apoptosis of TILs [78]. In many other reports, the fas ligand expressed was shown to be functional, i.e. its ligation of fas resulted in apoptosis of the target cell: for example, in breast and cervical cancer [28, 99]. In esophageal cancer, up-regulation of fas ligand and down-regulation of fas was found to be an early indicator of progression [52]; in this cancer, fas ligand was also found to be functional in triggering apoptosis of the TILs [11]. Longitudinal studies in melanoma revealed that fas-ligand expression by primary tumour was weak and rare, whereas in metasta-

ses, including those of these primary tumours, fas-ligand expression was stronger and commoner [148]. In gastric carcinoma, a correlation between tumour fas-ligand positivity, lymph node metastasis, and level of apoptosis in TILs was found [100]. However, in oral and oropharyngeal squamous cell carcinoma, no correlation was reported between fas or fas-ligand expression by the tumour and clinicopathological factors. Nonetheless, there was a correlation between fas-ligand expression and IL-10 (and GM-CSF) expression [44]. Direct evidence of a role for fas ligand in tumour escape is nonetheless hard to come by; in one attempt intratumourally transfected fas ligand antisense did result in reduction of tumour growth and metastasis, but the exact mechanism was not detailed [104]. Animal models demonstrate a potential clinical impact of these types of findings, where regressor and progressor variants of the same tumour can be distinguished by their level of fas-ligand expression (and MHC class II expression, which may induce anergy) [15]. These important facets of tumour-host interaction continue to be discussed in a lively manner [152, 163].

T-cell anergy

The induction of T-cell nonresponsiveness without destroying them and thereby possibly triggering compensatory responses on the part of the host probably contributes to a large degree to tumour escape. Even highly effective antigen-presenting cells such as DCs can be subverted by tumour products, eg. IL-10, to anergise rather than activate antitumour cells [142, 143], as mentioned above. Anergy induction is antigen-specific and is an early event associated with tumour progression [141]. Naturally occurring peptide sequences from endogenous as well as foreign proteins can act as partial agonists for the melanoma antigen MART-1/Melan-A (27–35) and anergise antitumour T cells by cross-presentation [86]. Moreover, the presence of such anergy-inducing peptides on the melanoma surface can prevent T-cell activation by immunodominant peptides [19].

On the other hand, recent investigations using HLA-A2/Melan-A (27–35) tetramers to visualise antigen-specific T cells revealed that in patients where antigen-specific cells expressed a $CCR7^{+}CD45RO^{-}$ (''naïve'') phenotype, there was a lack of response to the peptide in vitro. In contrast, where the $tetramer^{+}$ cells were $CCR7^{-}CD45RO^{+}$ there was a response [37]. This rather suggests lack of activation of antigen-specific cells in nonresponders, not activation and anergy induction. However, potentially dangerous for immunotherapy, under certain circumstances, anergy can also be induced by vaccination with immunogenic peptides representing tumour antigens [150]. This may be prevented by engineering stimulation via CD40-CD40L interactions [33], or other costimuli [164].

The in vivo relevance of these mechanisms in a clinical context has recently become susceptible to analysis by employing tetramer technology to identify tumour antigen–specific T cells in patients. Thus, the use of soluble tetramer/peptide complexes between HLA-A2 and common melanoma antigens such as tyrosinase (368–376) allow the direct demonstration of clonally expanded antigen-specific CD8 cells in melanoma patients. These effector cells were demonstrated to be anergic, being unable to lyse target cells or secrete cytokines on activation [81]. Similar clonal expansions have been found under other conditions of chronic antigenic stress, especially in aging where the driving antigenic force is likely to be persistent herpes virus infection [70, 106, 107].

Induction of suppressor cells

The recent renaissance of interest in suppressor cells has lead to the reinterpretation of many older data, which in the meantime had been dismissed as artifactual (for review, see [97]). The realisation that $CD4^{+}CD25^{+}$ regulatory cells play an important role in many aspects of immunological tolerance has led to attention being focused on such cells also in cancer (for review, see [128]). Potential treatment modalities may be developed following this realisation. In an animal model, injection of CD25 mAb preferentially depletes $CD25^{+}CD4$ cells and can prevent tumour progression [105]. Consistent with these data, Shimizu et al. reported that unresponsiveness to a variety of tumours in mice can be prevented by removing ''naturally'' activated (i.e. $CD25^{+}$) $CD4^{+}$ cells [139]. The remaining $CD4^{+}CD25^{-}$ cells were found also to proliferate to MHC class II^{+} self-peptides on autologous APCs, suggesting that tolerance to self, including tumours, had been broken.

T_H2-type cells can also be considered to have suppressive functions in that they secrete IL-4 and IL-10 as potentially down-regulatory cytokines. Such cells have also been identified among melanoma TILs, and could act as negative regulatory cells, although they themselves also specifically lysed autologous tumour cells in 18-h (i.e. long-term) cytotoxicity assays [71]. Along these lines, it has also been found that soluble products from NSCLC can induce IL-10 production in normal human PBMCs [63]. This was found to be caused by the PGE_2 secreted by the cancer cells; neutralisation of the secreted IL-10 enhanced IFN-γ production, suggesting a negative autocrine loop triggered by cancer cell–derived PGE_2. Intervention with prostaglandin blockers may therefore be beneficial, as has been reported for COX-2 inhibition in a rat model [145].

Alterations in signal-transducing molecules

Direct effects on T cells

The original observation that T-cell signal transduction is compromised in tumour-bearers [95] has subse-

quently been confirmed and extended to a variety of human tumours, including renal, colorectal, ovarian, liver, gastric, oral, prostate, pancreatic and cervical carcinomas, glioblastomas and melanomas (for review, see [162]). Of particular interest is the repeatedly documented correlation between these alterations and the disease stage in many different cancers. In mice, resection of tumour late after inoculation could still result in reappearance of an immune response, and normalisation of p56lck expression, a hallmark of this dysregulated state [131]. As even large tumour burdens in mice may still have effects limited to the locality, and do not cause systemic suppression [122], there may be hope of manipulation here to restore T-cell responsiveness. Down-regulated TCR signal transduction may be paralleled by down-regulation of CD28 [58]. This may reflect T-cell replicative senescence caused by continuous antigen activation, which could contribute to tumour escape from immunosurveillance [39, 109]. These correlations indicate that loss of ζ chain, or abnormal association between ζ chains and other CD3 components, might explain the observed gradual decline of cell-mediated responses in patients and experimental animals with progressing tumours. However, under certain conditions, extinction of ζ-signalling may not inhibit T-cell responses [6, 137], and decreased levels of CD3ζ chain in cancer patients may not correlate with their proliferative or cytotoxic capacity [25]. Conversely, it has been reported that T cells from PBMCs in early breast cancer patients do not show ζ chain deficiencies but are nonetheless functionally compromised [103]. Hence, there is some controversy still also in this area. However, where observed, the presumption is that prevention or reversal would be a good thing. In CMLs, for example, the majority of patients' T cells were indeed found to be CD3ζ deficient, which could be at least partially reversed by stimulation with CD3 mAb, IL-2 and IFN-α [24]. Whether the same sort of manipulation would be effective in vivo is also controversial. However, decreased CD3ζ in three patients with myeloid malignancies after successful remission induction showed normalisation of the TCRs [14]. A study of 26 RCC patients treated with IL-2, IFN-α and LAK cells revealed posttreatment improvement of low ζ-chain expression in 62% of the patients [51]. Moreover, 4/5 achieving a complete response normalised ζ (and $p56^{lck}$), whereas only 2/7 patients with progressive disease did so [51]. These reports therefore suggest that under certain conditions the defect in CD3 ζ expression might be reversible in vivo.

Effects via macrophages

The possibility that a mechanism of action of suppressor macrophages may be to induce alterations in signal transducing molecules has recently emerged from studies in murine and human systems. Macrophages with the capacity to suppress immune responses in tumour-bearing hosts have been extensively described before [2, 3, 90]. Aoe et al. [5] described the ability of tumour-infiltrating macrophages to decrease CD3ζ expression even on freshly isolated normal T cells. This effect is not tumour-specific, but may be a normal consequence of activation; thus zymosan/LPS-activated but not unactivated normal macrophages also induced CD3ζ down-regulation. However, this phenomenon does occur in cancer patients; Kono et al. [75] showed that macrophages isolated from metastatic lymph nodes of melanoma patients were able to down-regulate CD3 ζ levels in autologous PBLs. Again, this was not tumour-specific, because LPS-stimulated monocytes from normal PBMCs did the same. Because treatment with catalase prevented this, and H_2O_2 duplicated it, it was concluded that reactive oxygen metabolites produced by activated monocytes were responsible for ζ chain down-regulation [75]. The final mechanism of action of this oxidative stress-induced CD3 ζ loss may be via activation of components of the apoptotic pathway. Thus, oxidative stress triggers many cellular responses including proapoptotic factors such as p53; indeed, in a model system, loss of CD3 ζ chain may be directly mediated by one of the enzymes intimately involved in the apoptotic pathway, caspase-3 [48]. Moreover, the induction of apoptosis in T cells by fas-ligand–bearing ovarian carcinoma cells is accompanied by ζ down-regulation, and inhibitors of fas or apoptosis prevent this [121]. Moreover, it may well be the memory-phenotype cells, representing the antitumour effectors, which are most susceptible to oxidative stress [88].

These observations therefore argue that chronic inflammatory conditions in advanced cancer and in certain infectious and autoimmune conditions will alter the redox potential of macrophages, causing them to exert an immunosuppressive effect on the host immune system via secretion of factors such as H_2O_2. These factors will rapidly shut off the effector functions of CTL and NK cells. Research aimed at developing drugs which can counteract suppression of antitumour activity and which should be given in combination with immunotherapy should provide new and promising avenues for the treatment of cancer.

Immune stimulation

It has been repeatedly suggested that the immune system can exert a bipolar effect on tumours, often encouraging their growth [55, 115, 116, 118]. A striking recent demonstration of this phenomenon is the observation of enhanced growth of tumours in cancer-prone mice immunised with ras mutant peptides [140]. The progression of tumour development may even be dependent upon immune responses in at least some models, as shown by Hammond et al. [60]. Here, the rapidity and progression of carcinogen-induced guinea pig tumours was directly

correlated with the immune status of the animals. A fully competent immune system furthered tumour progression, a fully incompetent one did not, and a partly competent one lay between the two extremes. As has been pointed out [119], this kind of phenomenon might explain the paradoxical observations that certain types of human melanoma which are usually curable have a bad prognosis if and only if they show signs of spontaneous regression. A potential clinical relevance for these findings may be found in accumulating data on tumour incidence in immunosuppressed transplant recipients. Stewart et al. [144] found a reduced risk of breast cancer (but not other cancers) in a very large number of women with heart or kidney transplants.

Cytokines produced by T cells reacting to the tumour may well encourage tumour growth, especially in the case of hematopoietic tumours, e.g. B-CLL respond to IL-4 produced by T cells. IL-4 protects the tumour cells from apoptosis and acts as a growth factor [29]. Receptors for IL-4 [120] may be even more widespread than those for IL-2 and be important for either enhancing or inhibitory effects of immune activity on tumour growth [30]. In CMLs, class II–restricted T cells specific for b3/a2 fusion products enhanced tumour cell colony formation, *despite* their concurrent cytotoxicity [167]. Receptors for IL-10 have been found on melanoma cells and it has been reported that IL-10 may function as a growth-stimulating factor for melanoma as well as reducing cell surface expression of HLA and adhesion molecules [169]. In this case, melanoma cells may also produce the IL-10 themselves, making it an autocrine growth factor; but as alluded to above, infiltrating T cells may provide a rich source of IL-10 as well. A further remarkable example of immunostimulation was reported recently where mucosa-associated B-cell lymphomas develop secondary to *H. pylori* infection in the stomach; their growth was shown to depend on the presence of *H. pylori*-specific $CD4^+$ T cells [77]. Similarly, but without direct evidence, it has been suggested that the pathogenesis of hepatocellular carcinoma is dependent upon the immune response to HBV [102]. Novel and unsuspected mechanisms continue to be discovered, as illustrated by the recent finding that a T cell and monocyte-proinflammatory cytokine identified as macrophage migration inhibitory factor (MIF) inhibits the tumour suppressor activity of p53 [65].

Mechanisms other than cytokine production may also be involved in immunostimulation of the tumour. An intriguing report showed that many melanoma cells express CD40, which was on occasion up-regulatable by IFN-γ. While CD40 may engage CD154 on activated T cells and possibly deliver costimulatory signals, it is well known that on B cells CD40 itself delivers stimulatory signals required for target cell activation. According to Thomas et al. [149] the same may be true in melanoma, where ligating CD40 with mAb resulted in enhanced cell division. Thus, antimelanoma cells expressing CD154 (CD40-ligand) may interact with melanoma cells and directly stimulate them via CD40. Another aspect of immunostimulation of tumour growth is represented by the finding that TILs can also secrete angiogenic factors contributing to vascularisation of the tumours (basic fibroblast growth factor) and factors directly stimulating tumour cells (heparin-binding epidermal growth factor-like GF) [114]. TILs may also secrete other factors which indirectly assist the growth of tumour, e.g. vascular endothelial growth factor, which enhances angiogenesis [43]. In this study, in situ hybridisation showed that T cells infiltrating bladder and prostate cancer expressed VEGF mRNA and protein, and that isolated T cells could secrete bioactive VEGF. Activated macrophages may also stimulate enhanced VEGF and IL-8 production by melanoma cells, via a TNF/IL-1–dependent pathway; indeed the degree of macrophage infiltration has been reported to correlate with tumour stage and angiogenesis in melanoma [151]. Certainly, increased serum levels of VEGF, IL-8, bFGF and angiogenin do correlate with advanced disease state and degree of tumour burden [154]. Indeed, one of the requirements for $CD4^+$ cells in tumour rejection may be their production of IFN-γ, which results in blockade of tumour angiogenesis; if the tumour fails to respond to IFN-γ, e.g. by down-regulating IFN-γR, or by expressing factors blocking IFN-γ activity at downstream signalling pathways [165], it can escape this effect [10]. Indeed, IFN-γ may represent a critical regulatory cytokine for tumour control, also contributing to counteracting enhancement of tumour progression by T- and B-cell products. It appears that without IFN-γ, even when antitumour effectors are generated, they may not be able to home in properly to the tumour [101].

Tumours may also subvert the immune response by expressing receptors for T-cell growth factors such as IL-2. Absorption of IL-2 secreted by antitumour T cells could induce anergy. Moreover, tumours themselves might even be able to use IL-2 for their growth [17], so that expression of the IL-2R has been associated with higher levels of proliferation but increased drug resistance in some tumours [79]. The potential clinical impact of these findings is illustrated by a case report of a melanoma patient whose tumour progressed and metastasis increased during IL-2/IFN-α therapy [61]. As IL-2–based immunotherapy is effective in only a small minority of patients, and many reports record progressive disease in the majority, such immunoenhancement may be more common than usually accepted. McMillan et al. [92] previously reported that the majority of solid tumours express IL-2R β but not IL-2R α chains and some can respond to IL-2 by increasing growth rates, and this was blocked by anti-IL-2 Ab. On the other hand, some tumour cells expressing IL-2R can actually be blocked in their proliferation and not stimulated by IL-2 [161, 168]. The reasons for these differences are not clear; possibly they relate to different histological types tested (SCCHN and gastric blocked; melanoma and lung stimulated). In any event, it is clear that use of IL-2–based immunotherapy may be a risky business, and that the clinical experience that only a minority of patients responds while most progress may reflect this variation.

Concluding remarks

Tumours are immunogenic but escape complete destruction by the immune system by the main strategies of invisibility (down-regulation of recognisable targets) and subversion (both by nullifying attacking cells and by utilising them and their products to their own growth advantage). Overcoming the last hurdle to successful cancer immunotherapy will require identifying and abrogating each of these escape mechanisms.

Acknowledgements Experimental work in the author's laboratory was supported by the Deutsche Forschungsgemeinschaft (Pa 361/5-3, Pa 361/7-1), the Deutsche Krebshilfe (10-1173-Pa3, 10-1698-Pa5), and the Dieter Schlag Foundation; collaborations were supported by EU projects "ESTDAB" (QLRI-CT-2001-01325), "OISTER" (QLGI-CT-2002-00668), ImAginE (QLK6-CT-1999-02031) and T-CIA (QLK6-CT-2002-02283).

References

1. Aarli A, Kristoffersen EK, Jensen TS, Ulvestad E, Matre R (1997) Suppressive effect on lymphoproliferation in vitro by soluble annexin II released from isolated placental membranes. Am J Reprod Immunol 38:313
2. Alleva DG, Burger CJ, Elgert KD (1993) Interferon-gamma reduces tumour-induced macrophage-mediated suppression: role of prostaglandin-E2 and tumour necrosis factor-alpha. Immunopharmacology 25:215
3. Alleva DG, Walker TM, Elgert KD (1995) Induction of macrophage suppressor activity by fibrosarcoma-derived transforming growth factor-beta 1: contrasting effects on resting and activated macrophages. J Leukocyte Biol 57:919
4. Amiot L, Onno M, Lamy T, Dauriac C, Le Prise PY, Fauchet R, Drenou B (1998) Loss of HLA molecules in B lymphomas is associated with an aggressive clinical course. Br J Haematol 100:655
5. Aoe T, Okamoto Y, Saito T (1995) Activated macrophages induce structural abnormalities of the T cell receptor-CD3 complex. J Exp Med 181:1881
6. Ardouin L, Boyer C, Gillet A, Trucy J, Bernard AM, Nunes J, Delon J, Trautmann A, He HT, Malissen B, Malissen M (1999) Crippling of CD3-zeta ITAMs does not impair T cell receptor signaling. Immunity 10:409
7. Atassi T, Thuluvath PJ (2003) Risk of colorectal adenoma in liver transplant recipients compared to immunocompetent control population undergoing routine screening colonoscopy. J Clin Gastroenterol 37:72
8. Bai XF, Liu J, Li O, Zheng P, Liu Y (2003) Antigenic drift as a mechanism for tumour evasion of destruction by cytolytic T lymphocytes. J Clin Invest 111:1487
9. Barzegar C, Meazza R, Pereno R, Pottin-Clemenceau C, Scudeletti M, Brouty-Boye D, Doucet C, Taoufik Y, Ritz J, Musselli C, Mishal Z, Jasmin C, Indiveri F, Ferrini S, Azzarone B (1998) IL-15 is produced by a subset of human melanomas, and is involved in the regulation of markers of melanoma progression through juxtacrine loops. Oncogene 16:2503
10. Beatty GL, Paterson Y (2000) IFN-gamma can promote tumour evasion of the immune system in vivo by down-regulating cellular levels of an endogenous tumour antigen. J Immunol 165:5502
11. Bennett MW, O'Connell J, O'Sullivan GC, Brady C, Roche D, Collins JK, Shanahan F (1998) The Fas counterattack in vivo: apoptotic depletion of tumour-infiltrating lymphocytes associated with Fas ligand expression by human esophageal carcinoma. J Immunol 160:5669
12. Bergmann-Leitner ES, Abrams SI (2000) Influence of interferon gamma on modulation of Fas expression by human colon carcinoma cells and their subsequent sensitivity to antigen-specific CD8+ cytotoxic T lymphocyte attack. Cancer Immunol Immunother 49:193
13. Bergmann-Leitner ES, Abrams SI (2001) Positive and negative consequences of soluble Fas ligand produced by an antigen-specific CD4+ T cell response in human carcinoma immune interactions. Cell Immunol 209:49
14. Buggins AG, Hirst WJ, Pagliuca A, Mufti GJ (1998) Variable expression of CD3-zeta and associated protein tyrosine kinases in lymphocytes from patients with myeloid malignancies. Br J Haematol 100:784
15. Byrne SN, Halliday GM (2003) High levels of Fas ligand and MHC class II in the absence of CD80 or CD86 expression and a decreased CD4+ T cell Infiltration, enables murine skin tumours to progress. Cancer Immunol Immunother 52:396
16. Cabrera T, Lopez-Nevot MA, Gaforio JJ, Ruiz-Cabello F, Garrido F (2003) Analysis of HLA expression in human tumour tissues. Cancer Immunol Immunother 52:1
17. Capelli E, Civallero M, Barni S, Ceroni M, Nano R (1999) Interleukin-2 induces the growth of human glioblastoma cells in culture. Anticancer Res 19:3147
18. Carbone E, Terrazzano G, Ruggiero G, Zanzi D, Ottaiano A, Manzo C, Karre K, Zappacosta S (1999) Recognition of autologous dendritic cells by human NK cells. Eur J Immunol 29:4022
19. Carrabba MG, Castelli C, Maeurer MJ, Squarcina P, Cova A, Pilla L, Renkvist N, Parmiani G, Rivoltini L (2003) Suboptimal activation of CD8+ T cells by melanoma-derived altered peptide ligands: role of Melan-A/MART-1 optimized analogues. Cancer Res 63:1560
20. Cerwenka A, Lanier LL (2003) NKG2D ligands: unconventional MHC class I-like molecules exploited by viruses and cancer. Tissue Antigens 61:335
21. Chappell DB, Restifo NP (1998) T cell-tumour cell: a fatal interaction? Cancer Immunol Immunother 47:65
22. Chau GY, Wu CW, Lui WY, Chang TJ, Kao HL, Wu LH, King KL, Loong CC, Hsia CY, Chi CW (2000) Serum interleukin-10 but not interleukin-6 is related to clinical outcome in patients with resectable hepatocellular carcinoma. Ann Surg 231:552
23. Chaux P, Moutet M, Faivre J, Martin F, Martin M (1996) Inflammatory cells infiltrating human colorectal carcinomas express HLA class II but not B7-1 and B7-2 costimulatory molecules of the T-cell activation. Lab Invest 74:975
24. Chen X, Woiciechowsky A, Raffegerst S, Schendel D, Kolb HJ, Roskrow M (2000) Impaired expression of the CD3-zeta chain in peripheral blood T cells of patients with chronic myeloid leukaemia results in an increased susceptibility to apoptosis. Br J Haematol 111:817
25. Choi SH, Chung EJ, Whang DY, Lee SS, Jang YS, Kim CW (1998) Alteration of signal-transducing molecules in tumour-infiltrating lymphocytes and peripheral blood T lymphocytes from human colorectal carcinoma patients. Cancer Immunol Immunother 45:299
26. Chouaib S, Thiery J, Gati A, Guerra N, El Behi M, Dorothee G, Mami-Chouaib F, Bellet D, Caignard A (2002) Tumour escape from killing: role of killer inhibitory receptors and acquisition of tumour resistance to cell death. Tissue Antigens 60:273
27. Ciavarra RP, Brown RR, Holterman DA, Garrett M, Glass WF 2nd, Wright GL Jr, Schellhammer PF, Somers KD (2003) Impact of the tumour microenvironment on host infiltrating cells and the efficacy of flt3-ligand combination immunotherapy evaluated in a treatment model of mouse prostate cancer. Cancer Immunol Immunother 52:535
28. Contreras DN, Krammer PH, Potkul RK, Bu P, Rossi JL, Kaufmann AM, Gissmann L, Qiao L (2000) Cervical cancer cells induce apoptosis of cytotoxic T lymphocytes. J Immunother 23:67
29. Dancescu M, Rubio-Trujillo M, Biron G, Bron D, Delespesse G, Sarfati M (1992) Interleukin-4 protects chronic lympho-

cytic leukemic B-cells from death by apoptosis and upregulates Bcl-2 expression. J Exp Med 176:1319
30. Debinski W, Puri RK, Kreitman RJ, Pastan I (1993) A wide range of human cancers express interleukin-4 (IL4) receptors that can be targeted with chimeric toxin composed of IL4 and pseudomonas exotoxin. J Biol Chem 268:14065
31. de Vita F, Orditura M, Galizia G, Romano C, Roscigno A, Lieto E, Catalano G (2000) Serum interleukin-10 levels as a prognostic factor in advanced non-small cell lung cancer patients. Chest 117:365
32. de Waal Malefyt R, Abrams J, Bennett B, Figdor CG, de Vries JE (1991) Interleukin-10 (IL-10) inhibits cytokine synthesis by human monocytes—an autoregulatory role of IL-10 produced by monocytes. J Exp Med 174:1209
33. Diehl L, den Boer AT, Schoenberger SP, van der Voort EI, Schumacher TN, Melief CJ, Offringa R, Toes RE (1999) CD40 activation in vivo overcomes peptide-induced peripheral cytotoxic T-lymphocyte tolerance and augments anti-tumour vaccine efficacy. Nature Med 5:774
34. Dong H, Strome SE, Salomao DR, Tamura H, Hirano F, Flies DB, Roche PC, Lu J, Zhu G, Tamada K, Lennon VA, Celis E, Chen L (2002) Tumour-associated B7-H1 promotes T-cell apoptosis: a potential mechanism of immune evasion. Nat Med 8:793
35. Dowlati A, Levitan N and Remick SC (1999) Evaluation of interleukin-6 in bronchoalveolar lavage fluid and serum of patients with lung cancer. J Lab Clin Med 134:405
36. Dudley ME, Roopenian DC (1996) Loss of a unique tumour antigen by cytotoxic T lymphocyte immunoselection from a 3-methylcholanthrene-induced mouse sarcoma reveals secondary unique and shared antigens. J Exp Med 184:441
37. Dunbar PR, Smith CL, Chao D, Salio M, Shepherd D, Mirza F, Lipp M, Lanzavecchia A, Sallusto F, Evans A, Russell-Jones R, Harris AL, Cerundolo V (2000) A shift in the phenotype of melan-A-specific CTL identifies melanoma patients with an active tumour-specific immune response. J Immunol 165:6644
38. Dunn GP, Bruce AT, Ikeda H, Old LJ, Schreiber RD (2002) Cancer immunoediting: from immunosurveillance to tumour escape. Nat Immunol 3:991
39. Effros R, Pawelec G (1997) Replicative senescence of T lymphocytes: does the Hayflick Limit lead to immune exhaustion? Immunol Today 18:450
40. Favre-Felix N, Martin M, Maraskovsky E, Fromentin A, Moutet M, Solary E, Martin F, Bonnotte B (2000) Flt3 ligand lessens the growth of tumours obtained after colon cancer cell injection in rats but does not restore tumour-suppressed dendritic cell function. Int J Cancer 86:827
41. Fayad L, Keating MJ, Reuben JM, O'Brien S, Lee BN, Lerner S, Kurzrock R (2001) Interleukin-6 and interleukin-10 levels in chronic lymphocytic leukemia: correlation with phenotypic characteristics and outcome. Blood 97:256
42. Frassanito MA, Cusmai A, Iodice G, Dammacco F (2001) Autocrine interleukin-6 production and highly malignant multiple myeloma: relation with resistance to drug-induced apoptosis. Blood 97:483
43. Freeman MR, Schneck FX, Gagnon ML, Corless C, Soker S, Niknejad K, Peoples GE, Klagsbrun M (1995) Peripheral blood T lymphocytes and lymphocytes infiltrating human cancers express vascular endothelial growth factor: a potential role for T cells in angiogenesis. Cancer Res 55:4140
44. Fujieda S, Sunaga H, Tsuzuki H, Fan GK, Ito T, Sugimoto C, Saito H (2000) Expression of Fas (CD95) ligand is correlated with IL-10 and granulocyte colony-stimulating factor expression in oral and oropharyngeal squamous cell carcinoma. Cancer Lett 161:73
45. Fujihara T, Yashiro M, Inoue T, Sawada T, Kato Y, Ohira M, Nishiguchi Y, Ishikawa T, Sowa M, Chung KH (1999) Decrease in ICAM-1 expression on gastric cancer cells is correlated with lymph node metastasis. Gastric Cancer 2(4):221–225
46. Garcia-Lora A, Algarra I, Gaforio JJ, Ruiz-Cabello F, Garrido F (2001) Immunoselection by T lymphocytes generates repeated MHC class I-deficient metastatic tumour variants. Int J Cancer 91:109
47. Garcia-Lora A, Algarra I, Garrido F (2003) MHC class I antigens, immune surveillance, and tumour immune escape. J Cell Physiol 195:346
48. Gastman BR, Johnson DE, Whiteside TL, Rabinowich H (1999) Caspase-mediated degradation of T-cell receptor zeta-chain. Cancer Res 59:1422
49. Gaya SB, Rees AJ, Lechler RI, Williams G, Mason PD (1995) Malignant disease in patients with long-term renal transplants. Transplantation 59:1705
50. Giovarelli M, Musiani P, Modesti A, Dellabona P, Casorati G, Allione A, Consalvo M, Cavallo F, di Pierro F, De Giovanni C (1995) Local release of IL-10 by transfected mouse mammary adenocarcinoma cells does not suppress but enhances antitumour reaction and elicits a strong cytotoxic lymphocyte and antibody-dependent immune memory. J Immunol 155:3112
51. Gratama JW, Zea AH, Bolhuis RL, Ochoa AC (1999) Restoration of expression of signal-transduction molecules in lymphocytes from patients with metastatic renal cell cancer after combination immunotherapy. Cancer Immunol Immunother 48:263
52. Gratas C, Tohma Y, Barnas C, Taniere P, Hainaut P, Ohgaki H (1998) Up-regulation of Fas (APO-1/CD95) ligand and down-regulation of Fas expression in human esophageal cancer. Cancer Res 58:2057
53. Grothey A, Heistermann P, Philippou S, Voigtmann R (1998) Serum levels of soluble intercellular adhesion molecule-1 (ICAM-1, CD54) in patients with non-small-cell lung cancer: correlation with histological expression of ICAM-1 and tumour stage. Br J Cancer 77:801
54. Guerra N, Benlhassan K, Carayol G, Guillard M, Pardoux C, Chouaib S, Caignard A (1999) Effect of tumour growth factor-beta on NK receptor expression by allostimulated CD8(+) T lymphocytes. Eur Cytokine Netw 10:357
55. Guindi M (2000) Role of activated host T cells in the promotion of MALT lymphoma growth. Semin Cancer Biol 10:341
56. Hagenbaugh A, Sharma S, Dubinett SM, Wei SH, Aranda R, Cheroutre H, Fowell DJ, Binder S, Tsao B, Locksley RM, Moore KW, Kronenberg M (1997) Altered immune responses in interleukin 10 transgenic mice. J Exp Med 185:2101
57. Hahne M, Rimoldi D, Schroter M, Romero P, Schreier M, French LE, Schneider P, Bornand T, Fontana A, Lienard D, Cerottini J, Tschopp J (1996) Melanoma cell expression of Fas(Apo-1/CD95) ligand: Implications for tumour immune escape. Science 274:1363
58. Hakansson A, Gustafsson B, Krysander L, Hjelmqvist B, Rettrup B, Hakansson L (1999) On down-regulation of the immune response to metastatic malignant melanoma. Cancer Immunol Immunother 48:253
59. Halder TM, Bluggel M, Heinzel S, Pawelec G, Meyer HE, Kalbacher H (2000) Defensins are dominant HLA-DR-associated self-peptides from CD34(-) peripheral blood mononuclear cells of different tumour patients (Plasmacytoma, chronic myeloid leukemia). Blood 95:2890
60. Hammond WG, Benfield JR, Tesluk H, Johnson J R, Teplitz R L (1995) Tumour progression by lung cancers growing in hosts of different immunocompetence. Cancer J 8:130
61. Han D, Pottin-Clemenceau C, Imro MA, Scudeletti M, Doucet C, Puppo F, Brouty-Boye D, Vedrenne J, Sahraoui Y, Brailly H, Poggi A, Jasmin C, Azzarone B, Indiveri F (1996) IL2 triggers a tumour progression process in a melanoma cell line MELP, derived from a patient whose metastasis increased in size during IL2/IFNa biotherapy. Oncogene 12:1015
62. Holub M, Zakeri SM, Lichtenberger C, Pammer J, Paolini P, Leifeld L, Rockenschaub S, Wolschek MF, Steger G, Willheim M, Gangl A, Reinisch W (2003) Heterogeneous expression and regulation of CD40 in human hepatocellular carcinoma. Eur J Gastroenterol Hepatol 15:119
63. Huang M, Sharma S, Mao JT, Dubinett SM (1996) Non-small cell lung cancer-derived soluble mediators and prostaglandin

E2 enhance peripheral blood lymphocyte IL 10 transcription and protein production. J Immunol 157:5512
64. Huang SY, Ullrich SE, BarEli M (1999) Regulation of tumour growth and metastasis by interleukin-10: the melanoma experience. J Interferon Cytokine Res 19:697
65. Hudson JD, Shoaibi MA, Maestro R, Carnero A, Hannon GJ, Beach DH (1999) A proinflammatory cytokine inhibits p53 tumour suppressor activity. J Exp Med 190:1375
66. Hünig T (1983) T cell function and specificity in athymic mice. Immunol Today 4:84
67. Jager MJ, Hurks HM, Levitskaya J, Kiessling R (2002) HLA expression in uveal melanoma: there is no rule without some exception. Hum Immunol 63:444
68. Jodo S, Kobayashi S, Nakajima Y, Matsunaga T, Nakayama N, Ogura N, Kayagaki N, Okumura K, Koike T (1998) Elevated serum levels of soluble Fas/APO-1 (CD95) in patients with hepatocellular carcinoma. Clin Exp Immunol 112:166
69. Kageshita T, Hirai S, Ono T, Hicklin DJ, Ferrone S (1999) Down-regulation of HLA class I antigen-processing molecules in malignant melanoma—association with disease progression. Am J Pathol 154:745
70. Khan N, Shariff N, Cobbold M, Bruton R, Ainsworth JA, Sinclair AJ, Nayak L, Moss PA (2002) Cytomegalovirus seropositivity drives the CD8 T cell repertoire toward greater clonality in healthy elderly individuals. J Immunol 169:1984
71. Kharkevitch DD, Seito D, Balch GC, Maeda T, Balch CM, Itoh K (1994) Characterization of autologous tumour-specific T-helper 2 cells in tumour-infiltrating lymphocytes from a patient with metastatic melanoma. Int J Cancer 58:317
72. Kiertscher SM, Luo J, Dubinett SM, Roth MD (2000) Tumours promote altered maturation and early apoptosis of monocyte-derived dendritic cells. J Immunol 164:1269
73. Kim J, Modlin RL, Moy RL, Dubinett SM, McHugh T, Nickoloff BJ, Uyemura K (1995) IL-10 production in cutaneous basal and squamous cell carcinomas—a mechanism for evading the local T cell immune response. J Immunol 155:2240
74. Kim JA, Dayton MA, Aldrich W, Triozzi PL (1999) Modulation of CD4 cell cytokine production by colon cancer-associated mucin. Cancer Immunol Immunother 48:525
75. Kono K, Salazar-Onfray F, Petersson M, Hansson J, Masucci G, Wasserman K, Nakazawa T, Anderson P, Kiessling R (1996) Hydrogen peroxide secreted by tumour-derived macrophages down-modulates signal-transducing zeta molecules and inhibits tumour-specific T cell- and natural killer cell-mediated cytotoxicity. Eur J Immunol 26:1308
76. Koopman LA, Corver WE, van der Slik AR, Giphart MJ, Fleuren GJ (2000) Multiple genetic alterations cause frequent and heterogeneous human histocompatibility leukocyte antigen class I loss in cervical cancer. J Exp Med 191:961
77. Koulis A, Diss T, Isaacson PG, Dogan A (1997) Characterization of tumour-infiltrating T lymphocytes in B-cell lymphomas of mucosa-associated lymphoid tissue. Am J Pathol 151:1353
78. Koyama S, Maruyama T, Adachi S, Nozue M (1998) Expression of costimulatory molecules, B7-1 and B7-2 on human gastric carcinoma. J Cancer Res Clin Oncol 124:383
79. Kuhn DJ, Smith DM, Pross S, Whiteside TL, Dou QP (2003) Overexpression of interleukin-2 receptor alpha in a human squamous cell carcinoma of the head and neck cell line is associated with increased proliferation, drug resistance, and transforming ability.J Cell Biochem 89:824
80. Lauritzsen GF, Hofgaard PO, Schenck K, Bogen B (1998) Clonal deletion of thymocytes as a tumour escape mechanism. Int J Cancer 78:216
81. Lee PP, Yee C, Savage PA, Fong L, Brockstedt D, Weber JS, Johnson D, Swetter S, Thompson J, Greenberg PD, Roederer M, Davis MM (1999) Characterization of circulating T cells specific for tumour-associated antigens in melanoma patients. Nat Med 5:677
82. Lindelof B, Sigurgeirsson B, Gabel H, Stern RS (2000) Incidence of skin cancer in 5356 patients following organ transplantation. Br J Dermatol 143:513
83. Linderoth J, Jerkeman M, Cavallin-Stahl E, Kvaloy S, Torlakovic E (2003) Immunohistochemical expression of CD23 and CD40 may identify prognostically favorable subgroups of diffuse large B-cell lymphoma: a Nordic Lymphoma Group study. Clin Cancer Res 9:722
84. Link AA, Kino T, Worth JA, McGuire JL, Crane ML, Chrousos GP, Wilder RL, Elenkov IJ (2000) Ligand-activation of the adenosine A2a receptors inhibits IL-12 production by human monocytes. J Immunol 164:436
85. Liu L, Rich BE, Inobe J, Chen W, Weiner HL (1998) Induction of Th2 cell differentiation in the primary immune response: dendritic cells isolated from adherent cell culture treated with IL-10 prime naive CD4+ T cells to secrete IL-4. Int Immunol 10:1017
86. Loftus DJ, Squarcina P, Nielsen MB, Geisler C, Castelli C, Odum N, Appella E, Parmiani G, Rivoltini L (1998) Peptides derived from self-proteins as partial agonists and antagonists of human CD8+ T-cell clones reactive to melanoma/melanocyte epitope MART1(27-35). Cancer Res 58:2433
87. Maclean GD, Reddish MA, Longenecker BM (1997) Prognostic significance of preimmunotherapy serum CA27.29 (MUC-1) mucin level after active specific immunotherapy of metastatic adenocarcinoma patients. J Immunother 20:70
88. Malmberg KJ, Arulampalam V, Ichihara F, Petersson M, Seki K, Andersson T, Lenkei R, Masucci G, Pettersson S, Kiessling R (2001) Inhibition of activated/memory (CD45RO+) T cells by oxidative stress associated with block of NF-kappaB activation. J Immunol 167:2595
89. Malmberg KJ, Levitsky V, Norell H, de Matos CT, Carlsten M, Schedvins K, Rabbani H, Moretta A, Soderstrom K, Levitskaya J, Kiessling R (2002) IFN-gamma protects short-term ovarian carcinoma cell lines from CTL lysis via a CD94/NKG2A-dependent mechanism.J Clin Invest 110:1515
90. Mantovani A, Bottazzi B, Colotta F, Sozzani S, Ruco L (1992) The origin and function of tumour-associated macrophages. Immunol Today 13:265
91. Matsui K, O'Mara LA, Allen PM (2003) Successful elimination of large established tumours and avoidance of antigen-loss variants by aggressive adoptive T cell immunotherapy. Int Immunol 15:797
92. McMillan DN, Kernohan NM, Flett ME, Heys SD, Deehan DJ, Sewell HF, Walker F, Eremin O (1995) Interleukin 2 receptor expression and interleukin 2 localisation in human solid tumour cells in situ and in vitro: Evidence for a direct role in the regulation of tumour cell proliferation. Int J Cancer 60:766
93. Mellor AL, Munn DH (1999) Tryptophan catabolism and T-cell tolerance: immunosuppression by starvation? Immunol Today 20:469
94. Menon AG, Morreau H, Tollenaar RA, Alphenaar E, Van Puijenbroek M, Putter H, Janssen-Van Rhijn CM, Van De Velde CJ, Fleuren GJ, Kuppen PJ (2002) Down-regulation of HLA-A expression correlates with a better prognosis in colorectal cancer patients. Lab Invest. 82:1725
95. Mizoguchi H, O'Shea JJ, Longo DL, Loeffler CM, McVicar DW, Ochoa AC (1992) Alterations in signal transduction molecules in lymphocytes-T from tumour-bearing mice. Science 258:1795
96. Mocellin S, Panelli MC, Wang E, Nagorsen D, Marincola FM (2003) The dual role of IL-10. Trends Immunol 24:36
97. Morse MA, Clay TM, Mosca P, Lyerly HK (2002) Immunoregulatory T cells in cancer immunotherapy. Expert Opin Biol Ther 2:827
98. Mouawad R, Khayat D, Merle S, Antoine EC, Gil-Delgado M, Soubrane C (1999) Is there any relationship between interleukin-6/ interleukin-6 receptor modulation and endogenous interleukin-6 release in metastatic malignant melanoma patients treated by biochemotherapy? Melanoma Res 9:181
99. Muschen M, Moers C, Warskulat U, Even J, Niederacher D, Beckmann MW (2000) CD95 ligand expression as a mechanism of immune escape in breast cancer. Immunology 99:69

100. Nagashima H, Mori M, Sadanaga N, Mashino K, Yoshikawa Y, Sugimachi K (2001) Expression of Fas ligand in gastric carcinoma relates to lymph node metastasis. Int J Oncol 18:1157
101. Nakajima C, Uekusa Y, Iwasaki M, Yamaguchi N, Mukai T, Gao P, Tomura M, Ono S, Tsujimura T, Fujiwara H, Hamaoka T (2001) A role of interferon-gamma (IFN-gamma) in tumour immunity: T cells with the capacity to reject tumour cells are generated but fail to migrate to tumour sites in IFN-gamma-deficient mice. Cancer Res 61:3399
102. Nakamoto Y, Guidotti LG, Kuhlen CV, Fowler P, Chisari FV (1998) Immune pathogenesis of hepatocellular carcinoma. J Exp Med 188:341
103. Nieland JD, Loviscek K, Kono K, Albain KS, McCall AR, Potkul RK, Fisher SG, Velders MP, Petersson M, Kiessling R, Kast WM (1998) PBLs of early breast carcinoma patients with a high nuclear grade tumour unlike PBLs of cervical carcinoma patients do not show a decreased TCR zeta expression but are functionally impaired. J Immunother 21:317
104. Nyhus JK, Wolford C, Feng L, Barbera-Guillem E (2001) Direct in vivo transfection of antisense Fas-ligand reduces tumour growth and invasion. Gene Therapy 8:209
105. Onizuka S, Tawara I, Shimizu J, Sakaguchi S, Fujita T, Nakayama E (1999) Tumour rejection by in vivo administration of anti-CD25 (Interleukin-2 receptor alpha) monoclonal antibody. Cancer Res 59:3128
106. Ouyang Q, Wagner W, Walter S, Wikby A, Aubert G, Müller CA, Klatt T, Stevanovic S, Rammensee HG, Dodi T, Travers P, Pawelec G (2003) The age-related increase in $CD8^+$ T cells carrying receptors for an immunodominant Epstein-Barr virus (EBV) epitope is counterbalanced by decreased antigen-specific responsiveness. Mech Ageing Dev 124:477
107. Ouyang Q, Wagner W, Wikby A, Walter S, Aubert G, Dodi T, Travers P, Pawelec G (2003) Large numbers of dysfunctional $CD8^+$ T lymphocytes bearing receptors for a single dominant CMV epitope in the very old. J Clin Immunol 23:247
108. Paschen A, Mendez RM, Jimenez P, Sucker A, Ruiz-Cabello F, Song M, Garrido F, Schadendorf D (2003) Complete loss of HLA class I antigen expression on melanoma cells: a result of successive mutational events. Int J Cancer 103: 759
109. Pawelec G (1999) Tumour escape from the immune response: the last hurdle for successful immunotherapy of cancer? Cancer Immunol Immunother 48:343
110. Pawelec G, Hambrecht A, Rehbein A, Adibzadeh M (1996) Interleukin 10 protects activated human T lymphocytes against growth factor withdrawal-induced cell death but only anti-fas antibody can prevent activation-induced cell death. Cytokine 8:877
111. Pawelec G, Schlotz E, Rehbein A (1999) IFN-alpha regulates IL 10 production by CML cells in vitro. Cancer Immunol Immunother 48:430
112. Pawelec G, Barnett Y, Mariani E, Solana R (2002) Human CD4+ T cell clone longevity in tissue culture: lack of influence of donor age or cell origin. Exp Gerontol 37:265
113. Peguet-Navarro J, Sportouch M, Popa I, Berthier O, Schmitt D, Portoukalian J (2003) Gangliosides from human melanoma tumours impair dendritic cell differentiation from monocytes and induce their apoptosis. J Immunol 170:3488
114. Peoples GE, Goedegebuure PS, Smith R, Linehan DC, Yoshino I, Eberlein TJ (1995) T lymphocytes that infiltrate tumours and atherosclerotic plaques produce heparin-binding epidermal growth factor-like growth factor and basic fibroblast growth factor: a potential pathologic role. Proc Natl Acad Sci U S A 92:6547
115. Ponzio NM, Thorbecke GJ (2000) Requirement for reverse immune surveillance for the growth of germinal center-derived murine lymphomas. Semin Cancer Biol 10:331
116. Poppema S, van den Berg A (2000) Interaction between host T cells and Reed-Sternberg cells in Hodgkin lymphomas. Semin Cancer Biol 10:345
117. Powrie F, Menon S, Coffman RL (1993) Interleukin-4 and interleukin-10 synergize to inhibit cell-mediated immunity in vivo. Eur J Immunol 23:3043
118. Prehn RT (1994) Stimulatory effects of immune reactions upon the growths of untransplanted tumours. Cancer Res 54:908
119. Prehn RT (1995) On the probability of effective anticancer vaccines. Cancer J 8:284
120. Puri RK, Finbloom DS, Leland P, Mostowski H, Siegel JP (1990) Expression of high-affinity IL-4 receptors on murine tumour infiltrating lymphocytes and their up-regulation by IL-2. Immunology 70:492
121. Rabinowich H, Reichert TE, Kashii Y, Gastman BR, Bell MC, Whiteside TL (1998) Lymphocyte apoptosis induced by Fas ligand-expressing ovarian carcinoma cells—Implications for altered expression of T cell receptor in tumour-associated lymphocytes. J Clin Invest 101:2579
122. Radoja S, Rao TD, Hillman D, Frey AB (2000) Mice bearing late-stage tumours have normal functional systemic T cell responses in vitro and in vivo. J Immunol 164:2619
123. Reichmann E (2002) The biological role of the Fas/FasL system during tumour formation and progression. Semin Cancer Biol 12:309
124. Restifo NP (2000) Not so Fas: re-evaluating the mechanisms of immune privilege and tumour escape. Nat Med 6:493
125. Richter G, Kruger-Krasagakes S, Hein G, Huls C, Schmitt E, Diamantstein T, Blankenstein T (1993) Interleukin-10 transfected into Chinese hamster ovary cells prevents tumour growth and macrophage infiltration. Cancer Res 53:4134
126. Riker A, Cormier J, Panelli M, Kammula U, Wang E, Abati A, Fetsch P, Lee KH, Steinberg S, Rosenberg S, Marincola F (1999) Immune selection after antigen-specific immunotherapy of melanoma. Surgery 126:112
127. Rodolfo M, Zilocchi C, Accornero P, Cappetti B, Arioli I, Colombo MP (1999) IL-4-transduced tumour cell vaccine induces immunoregulatory type 2 CD8 T lymphocytes that cure lung metastases upon adoptive transfer. J Immunol 163:1923
128. Sakaguchi S, Sakaguchi N, Shimizu J, Yamazaki S, Sakihama T, Itoh M, Kuniyasu Y, Nomura T, Toda M, Takahashi T (2001) Immunologic tolerance maintained by CD25+ CD4+ regulatory T cells: their common role in controlling autoimmunity, tumour immunity, and transplantation tolerance. Immunol Rev. 182:18
129. Salazar-Onfray F, Charo J, Petersson M, Freland S, Noffz G, Qin Z, Blankenstein T, Ljunggren HG, Kiessling R (1997) Down-regulation of the expression and function of the transporter associated with antigen processing in murine tumour cell lines expressing IL-10. J Immunol 159:3195
130. Salgado R, Junius S, Benoy I, Van Dam P, Vermeulen P, Van Marck E, Huget P, Dirix LY (2003) Circulating interleukin-6 predicts survival in patients with metastatic breast cancer.Int J Cancer 103:642
131. Salvadori S, Gansbacher B, Pizzimenti AM, Zier KS (1994) Abnormal signal transduction by T cells of mice with parental tumours is not seen in mice bearing IL-2-secreting tumours. J Immunol 153:5176
132. Sanchez-Rovira P, Jimenez E, Carracedo J, Barneto IC, Ramirez R, Aranda E (1998) Serum levels of intercellular adhesion molecule 1 (ICAM-1) in patients with colorectal cancer: Inhibitory effect on cytotoxicity. Eur J Cancer 34:394
133. Sarris AH, Kliche KO, Pethambaram P, Preti A, Tucker S, Jackow C, Messina O, Pugh W, Hagemeister FB, McLaughlin P, Rodriguez MA, Romaguera J, Fritsche H, Witzig T, Duvic M, Andreeff M, Cabanillas F (1999) Interleukin-10 levels are often elevated in serum of adults with Hodgkin's disease and are associated with inferior failure-free survival. Ann Oncol 10:433
134. Schreiber H, Wu TH, Nachman J, Rowley DA (2000) Immunological enhancement of primary tumour development and its prevention. Semin Cancer Biol 10:351
135. Seliger B, Maeurer MJ, Ferrone S (1997) TAP off—tumours on. Immunol Today 18:292

136. Seliger B, Atkins D, Bock M, Ritz U, Ferrone S, Huber C, Storkel S (2003) Characterization of human lymphocyte antigen class i antigen-processing machinery defects in renal cell carcinoma lesions with special emphasis on transporter-associated with antigen-processing down-regulation. Clin Cancer Res 9:1721
137. She J, Ruzek MC, Velupillai P, de Aos I, Wang B, Harn DA, Sancho J, Biron CA, Terhorst C (1999) Generation of antigen-specific cytotoxic T lymphocytes and regulation of cytokine production takes place in the absence of CD3 zeta. Int Immunol 11:845
138. Shen W, Ladisch S (2002) Ganglioside GD1a impedes lipopolysaccharide-induced maturation of human dendritic cells. Cell Immunol 220:125
139. Shimizu J, Yamazaki S, Sakaguchi S (1999) Induction of tumour immunity by removing CD25+ CD4+ T cells: a common basis between tumour immunity and autoimmunity. J Immunol 163:5211
140. Siegel CT, Schreiber K, Meredith SC, Beck-Engeser GB, Lancki DW, Lazarski CA, Fu YX, Rowley DA, Schreiber H (2000) Enhanced growth of primary tumours in cancer-prone mice after immunization against the mutant region of an inherited oncoprotein. J Exp Med 191:1945
141. Staveley-O'Carroll K, Sotomayor E, Montgomery J, Borrello I, Hwang L, Fein S, Pardoll D, Levitsky H (1998) Induction of antigen-specific T cell anergy: An early event in the course of tumour progression. Proc Natl Acad Sci U S A 95:1178–1183
142. Steinbrink K, Jonuleit H, Muller G, Schuler G, Knop J, Enk AH (1999) Interleukin-10-treated human dendritic cells induce a melanoma-antigen-specific anergy in CD8+ T cells resulting in a failure to lyse tumour cells. Blood 93:1634
143. Steinbrink K, Graulich E, Kubsch S, Knop J, Enk AH (2002) CD4+ and CD8+ anergic T cells induced by interleukin-10-treated human dendritic cells display antigen-specific suppressor activity. Blood 99:2468
144. Stewart T, Tsai SC, Grayson H, Henderson R, Opelz G (1995) Incidence of de-novo breast cancer in women chronically immunosuppressed after organ transplantation. Lancet 346:796
145. Stolina M, Sharma S, Lin Y, Dohadwala M, Gardner B, Luo J, Zhu L, Kronenberg M, Miller PW, Portanova J, Lee JC, Dubinett SM (2000) Specific inhibition of cyclooxygenase 2 restores antitumour reactivity by altering the balance of IL-10 and IL-12 synthesis. J Immunol 164:361
146. Stutman O (1970) Tumour development after 3-methylcholanthrene in immunologically-deficient nude mice. Science 183:534
147. Taga K, Cherney B, Tosato G (1993) IL-10 inhibits apoptotic cell death in human T-cells starved of IL-2. Int Immunol 5:1599
148. Terheyden P, Siedel C, Merkel A, Kampgen E, Brocker EB, Becker JC (1999) Predominant expression of Fas (CD95) ligand in metastatic melanoma revealed by longitudinal analysis. J Invest Dermatol 112:899
149. Thomas WD, Smith MJ, Si Z, Hersey P (1996) Expression of the co-stimulatory molecule CD40 on melanoma cells. Int J Cancer 68:795
150. Toes RE, Offringa R, Blom RJ, Melief CJ, Kast WM (1996) Peptide vaccination can lead to enhanced tumour growth through specific T-cell tolerance induction. Proc Natl Acad Sci U S A 93:7855
151. Torisu H, Ono M, Kiryu H, Furue M, Ohmoto Y, Nakayama J, Nishioka Y, Sone S, Kuwano M (2000) Macrophage infiltration correlates with tumour stage and angiogenesis in human malignant melanoma: possible involvement of TNF alpha and IL-1 alpha. Int J Cancer 85:182
152. Trapani JA (2002) Tumour-mediated apoptosis of cancer-specific T lymphocytes–reversing the "kiss of death"? Cancer Cell 2:169
153. Tsutsumi S, Kuwano H, Shimura T, Morinaga N, Mochiki E, Asao T (2000) Circulating soluble Fas ligand in patients with gastric carcinoma. Cancer 89:2560
154. Ugurel S, Rappl G, Tilgen W, Reinhold U (2001) Increased serum concentration of angiogenic factors in malignant melanoma patients correlates with tumour progression and survival. J Clin Oncol 19:577
155. Vera A, Gunson BK, Ussatoff V, Nightingale P, Candinas D, Radley S, David Mayer A, Buckels JA, McMaster P, Neuberger J, Mirza DF (2003) Colorectal cancer in patients with inflammatory bowel disease after liver transplantation for primary sclerosing cholangitis. Transplantation 75:1983
156. Viac J, Schmitt D, Claudy A (1997) CD40 expression in epidermal tumours. Anticancer Res 17:569
157. von Leoprechting A, van der Bruggen P, Pahl HL, Aruffo A, Simon JC (1999) Stimulation of CD40 on immunogenic human malignant melanomas augments their cytotoxic T lymphocyte-mediated lysis and induces apoptosis. Cancer Res 59:1287
158. Vora AR, Rodgers S, Parker AJ, Start R, Rees RC, Murray AK (1997) An immunohistochemical study of altered immunomodulatory molecule expression in head and neck squamous cell carcinoma. Br J Cancer 76:836
159. Wajant H, Pfizenmaier K, Scheurich P (2003) Non-apoptotic Fas signaling. Cytokine Growth Factor Rev 14:53
160. Watanabe N, Gavrieli M, Sedy JR, Yang J, Fallarino F, Loftin SK, Hurchla MA, Zimmerman N, Sim J, Zang X, Murphy TL, Russell JH, Allison JP, Murphy KM (2003) BTLA is a lymphocyte inhibitory receptor with similarities to CTLA-4 and PD-1. Nat Immunol 4:670
161. Weidmann E, Sacchi M, Plaisance S, Heo DS, Yasumura S, Lin WC, Johnson JT, Herberman RB, Azzarone B, Whiteside TL (1992) Receptors for interleukin-2 on human squamous cell carcinoma cell lines and tumour in situ. Cancer Res 52:5963
162. Whiteside TL (1999) Signaling defects in T lymphocytes of patients with malignancy. Cancer Immunol Immunother 48:346
163. Whiteside TL (2002) Tumour-induced death of immune cells: its mechanisms and consequences. Semin Cancer Biol 12:43
164. Wilcox RA, Flies DB, Zhu G, Johnson AJ, Tamada K, Chapoval AI, Strome SE, Pease LR, Chen L (2002) Provision of antigen and CD137 signaling breaks immunological ignorance, promoting regression of poorly immunogenic tumours. J Clin Invest 109:651
165. Willers J, Urosevic M, Laine E, Geertsen R, Kundig T, Burg G, Dummer R (2001) The interferon inhibiting cytokine IK is overexpressed in cutaneous T cell lymphoma derived tumour cells that fail to upregulate major histocompatibility complex class II upon interferon-gamma stimulation. J Invest Dermatol 116:874
166. Yang G, Hellstrom KE, Mizuno MT, Chen L (1995) In vitro priming of tumour-reactive cytolytic T lymphocytes by combining IL-10 with B7-CD28 costimulation. J Immunol 155:3897
167. Yasukawa M, Ohminami H, Kaneko S, Yakushijin Y, Nishimura Y, Inokuchi K, Miyakuni T, Nakao S, Kishi K, Kubonishi I, Dan K, Fujita S (1998) CD4+ cytotoxic T-cell clones specific for bcr-abl b3a2 fusion peptide augment colony formation by chronic myelogenous leukemia cells in a b3a2-specific and HLA-DR-restricted manner. Blood 92:3355
168. Yasumura S, Lin WC, Weidmann E, Hebda P, Whiteside TL (1994) Expression of interleukin 2 receptors on human carcinoma cell lines and tumour growth inhibition by interleukin 2. Int J Cancer 59:225
169. Yue FY, Dummer R, Geertsen R, Hofbauer G, Laine E, Manolio S, Burg G (1997) Interleukin-10 is a growth factor for human melanoma cells and down-regulates HLA class-1, HLA class-II and ICAM-1 molecules. Int J Cancer 71:630
170. Zavos G, Bokos J, Papaconstantinou J, Boletis J, Gazouli M, Pappas P, Kostakis A (2003) Study of "de novo" malignancies among Greek renal transplant recipients. Transplant Proc 35:1399

171. Zeidler R, Eissner G, Meissner P, Uebel S, Tampe R, Lazis S, Hammerschmidt W (1997) Downregulation of TAP-1 in B lymphocytes by cellular and Epstein-Barr virus-encoded Interleukin 10. Blood 90:2390

172. Zhang GJ, Adachi I (1999) Serum interleukin-6 levels correlate to tumour progression and prognosis in metastatic breast carcinoma. AntiCancer Res 19:1427