Metabolic disturbance and sensitivity to endotoxin in patients with advanced cancer: relationship to lymphocyte reactivity, tumour necrosis factor (TNF) production and survival

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SUMMARY
Increased TNF production and impaired lymphocyte function have been individually linked with metabolic disturbance, endotoxaemia and mortality in humans. The inter-relationship between these observations was investigated in humans with cancer. In 13 patients with metastatic colorectal cancer and seven healthy volunteers, observations (n = 20) included peripheral blood mononuclear cell (PBMC) TNF production, IL-2 production and phytohaemagglutinin (PHA) response; the acute-phase protein response (APPR) (serum C-reactive protein (CRP), albumin, CRP/albumin ratio), and survival. APPR correlated with survival (CRP, r = −0.689, P = 0.006; CRP/albumin, r = −0.758, P = 0.002; albumin, r = 0.655, P = 0.011), but not with TNF production. TNF production in response to in vitro endotoxin correlated with impaired lymphocyte function in patients (r = 0.567, P = 0.043) and in the whole group (r = 0.65, P = 0.001). The ratio (basal PBMC TNF production)/(lymphocyte function) correlated with CRP (r = 0.569, P = 0.042), CRP/albumin (r = 0.617, P = 0.025), endotoxin sensitivity (r = 0.567, P = 0.043) and survival (r = −0.545, P = 0.038) in patients, and the whole group (P < 0.002). Impaired lymphocyte function may influence TNF production, endotoxin sensitivity and metabolic disturbance in humans with cancer. (r = Spearman correlation coefficient.)

Keywords tumour necrosis factor IL-2 lymphocyte acute-phase proteins survival cancer

INTRODUCTION
Many patients with cancer develop metabolic dysfunction consisting of refractory weight loss, decreased appetite and altered metabolism of body protein and fat (cachexia) [1]. They are also relatively susceptible to sepsis [2,3]. These two phenomena (cachexia and sepsis) account for a significant proportion of cancer-related deaths [2,3], but their development appears to be unrelated to tumour bulk [1,4], and is in fact linked to the activity of monokines, e.g. IL-1 and IL-6, particularly TNF/cachectin [4–7].

While there is significant evidence to implicate TNF and endotoxin in the induction of these phenomena and the associated acute-phase response [6–12], serum levels of TNF or endotoxin have not been correlated directly with parameters reflecting cachexia, the acute-phase response or sepsis [13,14]. This may be related to the fact that sensitivity to TNF and endotoxins may vary, particularly in the tumour state [15,16].

In many conditions associated with sepsis and metabolic disturbance (e.g. cancer, burns, trauma, AIDS) in which TNF is thought to be an important mediator [17–19] lymphocyte function is frequently impaired [20–22]. Whether lymphocyte function alters sensitivity to, or production of TNF is unknown, but receptors for lymphocyte-derived substances, such as IL-2 and IL-4, are expressed on cells such as peripheral blood monocytes, which are highly potent in terms of TNF secretion [23,24]. Some of these cytokines, e.g. IL-4, may reduce monocytic production of TNF and IL-1 in response to in vitro endotoxin [24].

The present study was designed to investigate the relationships between lymphocyte function, TNF production, survival, and parameters reflecting cachexia and the acute-phase response of patients with advanced metastatic colorectal cancer. A further aim was to establish whether factors related to peripheral blood cell type and concentration, or the ability of these cells to produce TNF, might account for the expected differences in metabolic status and acute-phase protein response between older patients with metastatic cancer and healthy younger volunteers.

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PATIENTS AND METHODS

Subjects and protocol
With the approval of the Hospital Ethics Committee and informed patient consent, the study group consisted of 13 patients (11 males), median age 50 years (range 39–73 years), with biopsy-proven liver metastases, each of whom had a primary resection for colorectal cancer at least 6 months before the study. All had received chemotherapy (5-fluorouracil via the hepatic artery) 1 week before the study, and metastases accounted for a significant proportion of liver volume. All were out-patients with no evidence of gastrointestinal obstruction or clinical infection, and all were consuming a normal diet. Seven healthy male laboratory staff were also studied (median age 31 years, range 24–41 years). Three of these had experienced minor weight gain (<3%) over the previous 6 months.

Blood samples were drawn in the early morning from fasted patients and volunteers. For logistical reasons, the study was performed over 2 study days separated by 9 weeks. One patient and two volunteers were studied on both study days, and resulting data therefore consisted of 23 observations for most of the parameters studied.

Serum albumin, serum C-reactive protein (CRP) and CRP/albumin ratios were used as indices of the acute-phase response [25]. Routine haematology tests were performed. Weight change over the previous 6 months was assessed by questionnaire and patient records, and survival from day of study was noted for all patients.

Assessment of lymphocyte function
Two assays of in vitro lymphocyte function were used in the study, IL-2 production and phytohaemagglutinin (PHA)-induced blastogenesis.

Generation of IL-2 supernatants
Heparinized peripheral blood (20 ml) was separated over Ficoll as previously described [26]. Unless otherwise stated, reagents for cell washing and culture were obtained from Sigma Chemical Co (Poole, UK). Cells were counted and concentrations adjusted to 1 × 10⁶ cells/ml in medium with added fetal calf serum (FCS; 5%). Cells (100 µl) were then plated in microtitre plates and 20 µl of PHA (62.5 µg/ml) were added to triplicate wells and the final concentration in stimulus and control wells made up to 250 µl volumes with media. Following a 24-h incubation under standard conditions [26], supernatants were withdrawn and frozen at −20°C.

IL-2 assay
IL-2 concentration was determined using the CTLL-2 cell bioassay [27]. Cell viability was determined using a colorimetric method [28]. An IL-2 standard of 2.5 U/ml was incorporated in the assay for determination of sample IL-2 concentration. All samples were assayed on the same day.

Lymphocyte blastogenesis
Mononuclear cells were isolated by Ficoll density centrifugation [26] as above and concentrations adjusted to 1 × 10⁶ cells/ml in medium with added FCS (5%). Cells (100 µl) were then dispensed in microtitre plates. PHA (20 µl of 125 µg/ml) was added to each well at a final concentration of 10 µg/ml. Media were added to attain equal well volumes of 250 µl/well. Each assay was performed in triplicate and background wells, without PHA, were also used for each sample. Cultures were incubated under standard conditions [26]. Tritiated thymidine (³H-TdR), 1 µCi/well in 20 µl media, was added after 72 h and the plates removed after a further 16 h and frozen at −20°C. Cells were later harvested and uptake of ³H-TdR determined on a beta-counter (LKB Instruments, Gaithersburg, MD). The mean response in c/min for triplicate samples without PHA was subtracted from the mean of samples with PHA to yield the PHA response.

To eliminate interassay variation between both study days, percentage PHA response of each subject with respect to the mean of the five healthy volunteers studied on that day, was used as an index, rather than PHA response in c/min, which may be subject to daily variation.

Percentage volunteer PHA response for each subject was calculated by the formula: % volunteer PHA response = ((PHA response in c/min for each subject)/(mean PHA response in c/min for volunteers studied on the day)) × 100.

Peripheral blood mononuclear cell TNF production
Peripheral blood mononuclear cells (PBMC) were separated as above and plated in microtitre plates at 1 × 10⁶ cells/well in 200 µl medium (as above). Escherichia coli endotoxin 055-B5 (or saline) (Difco Labs, Detroit, MI), 20 µl to yield a final concentration of 1–25 µg/ml was added to each of triplicate wells to generate TNF-containing supernatants. Samples were incubated under the same conditions as above for 24 h, at which time cell-free supernatants were collected and frozen at −20°C.

In seven of the subjects (four patients and three volunteers) TNF production in response to a higher concentration of endotoxin (5 µg/ml) was also measured.

TNF bioassay
Supernatant cytotoxicity was titrated against the TNF-sensitive cell line WEHI 164 clone 13 [29] using a recombinant human TNF preparation as a standard. PBMC TNF production was then calculated in relation to the standard TNF preparation. The stimulation index (SI) for TNF production was calculated by the formula: SI for TNF (S/U) = amount of TNF generated in endotoxin-stimulated cultures/amount of TNF generated in cultures with saline (basal TNF production).

Statistical analysis
Dose–response curves from the IL-2 and TNF bioassays were analysed using the curve fitting program “ALLFIT” [30]. All parameters are expressed as medians with ranges of values and were compared between patients and volunteers using the Mann–Whitney test. Spearman tests were used to evaluate correlation coefficients. Significance was implied for P < 0.05.

RESULTS

Survival
Median patient survival was 144 days (range 5–679 days). Survival duration was significantly associated with increased serum albumin, decreased serum CRP, decreased CRP/albumin, and decreased leucocyte count (Table 1, Fig. 1). Survival did not correlate with weight loss (Table 1).

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Table 1. Relationship between immune and metabolic function, and survival in patients (n = 13) with metastatic colorectal cancer

<table>
<thead>
<tr>
<th>Variable</th>
<th>r</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP/albumin (ratio)</td>
<td>−0.758</td>
<td>0.002*</td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td>−0.689</td>
<td>0.006*</td>
</tr>
<tr>
<td>Albumin (g/l)</td>
<td>0.655</td>
<td>0.011*</td>
</tr>
<tr>
<td>Leucocyte count (x10⁹/l)</td>
<td>−0.67</td>
<td>0.012*</td>
</tr>
<tr>
<td>Basal PBMC TNF (pg/ml per million PBMC)</td>
<td>−0.534</td>
<td>0.049*</td>
</tr>
<tr>
<td>Weight loss (%)</td>
<td>0.15</td>
<td>0.608</td>
</tr>
</tbody>
</table>

* = Implies statistical significance.

r = Spearman correlation coefficient.

CRP, C-reactive protein; PBMC, peripheral blood mononuclear cells.

Weight loss, serum albumin and CRP values

Though all patients had similar tumours, large variations were noted in terms of weight loss (3–25%), serum CRP (8–180 mg/l) and albumin values (18–42 g/l). Median serum albumin levels for patients (31 g/l) were significantly reduced, and serum CRP concentrations (54 mg/l) and CRP/albumin ratios (2.1) were increased, compared with normal reference ranges for this population (albumin (39–46 g/l), CRP (<10 mg/l), CRP/albumin (<2.8)) and with volunteers.

Although weight loss correlated with decreased serum albumin levels (r = −0.62, P < 0.018), significant correlations were not observed between weight loss and CRP (P = 0.549) or CRP/albumin ratios (P = 0.399) in patients.

Haematology

Peripheral blood percentages of neutrophils, lymphocytes, monocytes, leucocytes or lymphocyte/lymphocyte ratios were not significantly different between patients and volunteers.

Cell culture concentrations

Percentages of monocytes and lymphocytes in Ficoll-prepared mononuclear cell populations were calculated from peripheral blood indices, and values are given as for those of peripheral blood, less neutrophil percentage, as the percentage of polymorphs after Ficoll preparation was found to amount to < 5% of the total cell number. No significant differences were observed between patients and volunteers.

IL-2 production

IL-2 production varied in patients (0.34 (0.6–1.2 U/ml)) and volunteers (0.9 (0.1–6 U/ml)) but was significantly less in patients (P = 0.03). In patients, IL-2 production failed to correlate with leucocyte count (P = 0.871), percentage of lymphocytes (P = 0.19), survival (P = 0.288), serum albumin (P = 0.254), CRP (r = −0.477, P = 0.08) or CRP/albumin ratio (r = −0.534, P = 0.06).

Lymphocyte blastogenesis

PHA responses correlated with IL-2 production for the whole group (r = 0.589, P < 0.004) and for patients (r = 0.683, P < 0.01), and was significantly less in patients (38 (9–80%)) compared with volunteers (100 (60–154)) (P < 0.0005). No correlations were observed in patients between PHA responses and CRP (P = 0.396), CRP/albumin ratio (P = 0.323), albumin (P = 0.766), basal TNF production (P = 0.52), percent lymphocytes (P = 0.169), leucocyte count (P = 0.199), or survival (P = 0.499).

TNF production

In both patients and volunteers, basal PBMC TNF production was variable and was not significantly different between patients and volunteers (Table 2). For the group as a whole (patients and volunteers), basal PBMC TNF production failed to correlate with the proportion of monocytes (P = 0.358) or lymphocytes (P = 0.355) in the culture pool, nor did it correlate with these indices in either group alone.

In patients, basal TNF production correlated weakly with survival (r = −0.534, P = 0.049) and leucocyte count (r = 0.676, P = 0.011), but not with CRP (P = 0.276), CRP/albumin (P = 0.125), weight loss (P = 0.964), serum albumin (P = 0.111), percentage circulating lymphocytes (P = 0.237) or neutrophils (P = 0.319).

TNF production in response to in vitro endotoxin

There was no significant difference in TNF production in response to in vitro endotoxin (1.25 μg/ml) (endotoxin sensitivity) between patients and volunteers (Table 2), nor was endotoxin sensitivity related to the proportion of monocytes in blood (P = 0.75) or culture (P = 0.318) in the whole group. In a significant number of patients (n = 5) and controls (n = 6), no increase in TNF production was noted in response to endotoxin challenge.

In the four patients and three controls in whom enough cells were present to examine responses to higher concentrations of endotoxin (5 μg/ml), SIs in patients (1.15 (0.92–1.98 pg/ml)) were similar to those of volunteers (0.93 (0.28–2.02 pg/ml)).

For all subjects, depressed lymphocyte function was associated with increased sensitivity to in vitro endotoxin, reflected in correlations between both the change in TNF production in response to endotoxin and the SI for TNF, and decreased IL-2 production.

Fig. 1. Association between survival and ratio C-reactive protein (CRP)/albumin (a), CRP (b) and albumin (c) in the patient group. r = Spearman correlation coefficient between absolute values. Survival is indicated in log form for illustration purposes.

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production and reduced PHA response (Table 3, Fig. 2). In patients alone the SI for TNF also correlated with impaired PHA response ($r = -0.567, P = 0.043$).

When higher concentrations of endotoxin ($5 \mu g/ml$) were used, SIs also correlated significantly with impaired lymphocyte function, i.e. IL-2 production ($r = 0.821, P = 0.023, n = 7$).

**TNF production/lymphocyte function**

Since increased sensitivity to endotoxin *in vitro* was related to impaired lymphocyte function (Table 3, Fig. 2), and since sensitivity to endotoxin often parallels sensitivity to TNF [15,16], indices were derived incorporating basal TNF production/lymphocyte function, to determine whether increased TNF activity *in vitro* might relate to impairment of *in vivo* lymphocyte function. In patients, one or both of these indices (TNF/IL-2 or TNF/PHA) correlated significantly with increased CRP, increased CRP/albumin, endotoxin sensitivity, and survival (Table 4, Figs 3 and 4).

For all subjects, these indices correlated with parameters which had been associated with impaired survival, i.e. increased CRP, CRP/albumin, and leucocyte count, and decreased albumin (Table 4, Fig. 5).

**DISCUSSION**

The magnitude of the acute-phase protein response in patients with metastatic colorectal cancer correlated with reduced survival in the present study and in previous studies of patients with other tumours [31]. Patients and volunteers showed similar TNF production and cell concentrations, and neither variable correlated with the presence or magnitude of the acute-phase protein response, and failed to separate the diverse groups in terms of outcome.

These results do not necessarily exclude a role for TNF in the acute-phase protein response, since *in vivo* TNF production in the subjects may have been affected by levels of circulating endotoxin [7,8,12,26] and *in vivo* sensitivity to TNF may increase in the cancer state [15]. Sensitivity to endotoxin may also vary, and in cancer appears to parallel sensitivity to TNF [15]. In the present study, variations in endotoxin sensitivity (*in vitro* TNF...)

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**Table 2. Peripheral blood mononuclear cell (PBMC) TNF production**

<table>
<thead>
<tr>
<th></th>
<th>Patients ($n = 14$)</th>
<th>Volunteers ($n = 9$)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>In vitro TNF production (basal)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pg/ml per million PBMC</td>
<td>119 (16–2100)</td>
<td>49 (19–402)</td>
<td>0.16</td>
</tr>
<tr>
<td>pg/ml per million monos</td>
<td>774 (112–10 500)</td>
<td>320 (9–1158)</td>
<td>0.10</td>
</tr>
<tr>
<td><strong>In vitro TNF production (endotoxin-stimulated)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in TNF production</td>
<td>$+23 (-77$ to $+770)$</td>
<td>$-7 (-3$ to $+15)$</td>
<td>0.18</td>
</tr>
<tr>
<td></td>
<td>$+76 (-98$ to $+3850)$</td>
<td>$-22 (-192$ to $+47)$</td>
<td>0.08</td>
</tr>
<tr>
<td>Stimulation index for TNF</td>
<td>1.1 (0.6–1.9)</td>
<td>0.9 (0.3–1.4)</td>
<td>0.23</td>
</tr>
</tbody>
</table>

**Comparison of (basal TNF/lymphocyte function)**

<table>
<thead>
<tr>
<th></th>
<th>Patients ($n = 14$)</th>
<th>Volunteers ($n = 9$)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNF/IL-2 ratio</td>
<td>426 (17–721)</td>
<td>114 (8–231)</td>
<td>0.001*</td>
</tr>
<tr>
<td>TNF/PHA ratio</td>
<td>5.3 (0.2–38.7)</td>
<td>0.5 (0.2–6.8)</td>
<td>0.001*</td>
</tr>
</tbody>
</table>

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**Table 3. Association between response to *in vitro* endotoxin and impaired *in vitro* lymphocyte function**

<table>
<thead>
<tr>
<th></th>
<th>IL-2 production</th>
<th>PHA response</th>
</tr>
</thead>
<tbody>
<tr>
<td>All subjects ($n = 23$)</td>
<td>$r$ value</td>
<td>$P$</td>
</tr>
<tr>
<td><strong>Change in TNF production</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TNF (pg/ml per million PBMC)</td>
<td>$-0.458$</td>
<td>0.032*</td>
</tr>
<tr>
<td>TNF (pg/ml per million monos)</td>
<td>$-0.556$</td>
<td>0.011*</td>
</tr>
</tbody>
</table>

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**Table 2. Peripheral blood mononuclear cell (PBMC) TNF production**

- $n$, Observations; stimulation index for TNF = PBMC TNF production in response to *in vitro* endotoxin ($1.25 \mu g/ml$) divided by PBMC TNF production without endotoxin; (pg/ml per million) = pg of TNF per ml of supernatant per million cells in culture; +, an increase in production; −, a decrease in production.
- PBMC, Peripheral blood mononuclear cells.

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**Table 3. Association between response to *in vitro* endotoxin and impaired *in vitro* lymphocyte function**

- $r$, Spearman correlation coefficient.
- * Implies statistical significance by Spearman test.

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production in response to endotoxin) were related to lymphocyte function rather than the presence of tumour, or variability in monocyte concentrations in blood or culture. Increased sensitivity to endotoxin, and TNF, may therefore be related to impaired lymphocyte function.

Increased ratios of TNF/lymphocyte function correlated with clinical disturbances normally attributed to TNF activity [7–12], with reduced survival, and with in vitro sensitivity to endotoxin. Improvement of lymphocyte function can prolong survival in animal models of conditions associated with endotoxaemia and increased TNF activity, e.g. Gram-negative sepsis, in whom mortality is related to impaired lymphocyte function [32–34]. Addition of IL-2 reduces in vitro PBMC TNF production in response to endotoxin [26]. These reports suggest a role for lymphocyte function in determining sensitivity to endotoxins and/or TNF.

This hypothesis may explain the variations in metabolic status in patients with similar tumours [1–3,26,31]; why patients with certain cancers, e.g. breast cancer, who are seldom immunosuppressed [35], rarely develop cachexia [1]; the lack of an acute-phase response in healthy subjects with endotoxaemia; and the poor correlation between serum endotoxin and TNF levels with outcome in immuno-suppressed patients [13,14], in whom impaired lymphocyte function may predict those at risk of death from sepsis [20,21].

While it is possible that tumour circulation may influence TNF production, tumour homogenates have not been shown to incite significant in vitro TNF production. Moreover, serum levels of TNF in humans rarely correlate with clinical abnormalities. Alternatively, other cytokines (IL-1 [5], IL-6 [6] and IL-8 [36]) known to influence inflammatory and metabolic processes [8,9] may be important mediators of the acute-phase response in cancer. However, since TNF stimulates IL-1, TNF, IL-6 and IL-8 production...
lymphocyte function may also indirectly regulate production of these other metabolically active monokines.

The index TNF/lymphocyte function was chosen for the following reasons. TNF has been implicated in the induction of cancer cachexia, the acute-phase response and sepsis [8–12]. Impaired lymphocyte function is related to death from Gram-negative sepsis [20,21,33], a phenomenon related to endotoxin sensitivity. In a large proportion of patients who suffer metabolic disturbance and in whom TNF activity is increased, depressed lymphocyte function is common [17–22,38]. Lymphocyte function may be impaired by age, diet, medication and the levels of circulating endotoxins [39], variables which were not strictly controlled in this study, but which might, in the light of our findings, have indirectly influenced monokine activity and metabolism.

Ficoll density centrifugation may not be optimal in separating pure mononuclear cells [40], and methods other than bioassays are available for cytokine assay. However, the methods employed in this study approximate those used in studies quoted, discussing links between impaired lymphocyte function, metabolic disturbance, TNF, and impaired survival in various conditions [7–9,13,14,20,21,33–35,39]. Correlations derived using TNF/lymphocyte activity involved different assessments of lymphocyte function, using different concentrations of stimulant (PHA) and assays of function (thymidine incorporation and bioassay). TNF production by PBMC was chosen, rather than serum levels or secretion by pure monocyte/macrophage cells, as the latter would have neglected the potential influence of lymphocytes on TNF production, while the former fails to consider the short half-life of, and variable sensitivity to, TNF [7,15,16].

Endotoxin is known to stimulate TNF production in vivo and in vitro [29,39]. In a further study, the index TNF/lymphocyte function was multiplied by the levels of circulating endotoxins. Highly significant correlations were observed between this new index (endotoxin × TNF/lymphocyte function) and factors which reflect altered metabolic state, i.e. CRP, albumin, CRP/albumin, weight loss, body mass index and lean body mass in nine of 12 subjects in this study in whom plasma endotoxin values were significant (unpublished data).

Tolerance to TNF and endotoxins in animals with tumour [15,41,42] renders them less sensitive to cachexia and sepsis, and allows them to survive far longer than those who exhibit normal sensitivity patterns to TNF and endotoxins. The induction of tolerance to TNF or endotoxins in humans might also result in a reduction of cachexia and inflammatory processes. Anti-endotoxin and anti-TNF antibodies have so far been relatively unsuccessful in dealing with endotoxin and TNF [43,44], perhaps because this technology disregards individual differences in sensitivity to endotoxins and TNF, and the fact that healthy subjects secrete TNF [26], and may occasionally have transient endotoxaemias.

Perhaps a study administering low concentrations of IL-2 to improve lymphocyte function might be appropriate. Such an approach improves lymphocyte function in patients with hepatitis B and AIDS [45,46], and in addition, a single dose of 36,000 units of IL-2 reduces TNF mRNA, IL-6 mRNA, and serum CRP in hepatitis B patients for 72 h [45]. Low dose IL-2 (< 250 U/mouse) reduces sensitivity to endotoxins in models of thermal injury, cancer cachexia and endotoxin hypersensitivity [34,35,47], and improves lymphocyte function in animals with burns in whom mortality following septic challenge is related to depressed lymphocyte function [32]. In contrast, high dose IL-2, which is usually toxic [48], is administered in tumour-targeted protocols in concentrations based on surface area, not immune function, with little regard for potential differences in pharmacological and physiological effects of cytokines.

In conclusion, these data suggest that a combination of factors, which include lymphocyte function and PBMC TNF production, may account for increased sensitivity to sepsis and metabolic disturbance in humans with cancer. Administration of physiological concentrations of IL-2 to immunosuppressed patients, in an attempt to improve lymphocyte function and reduce abnormalities associated with TNF and endotoxins, may be worthwhile. Current strategies seem unrewarding in these patients who are subject to an ongoing acute-phase protein response, a phenomenon which was associated with the ultimate demise of the patient group in this study.

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Lymphocyte function, TNF secretion and inflammation in humans

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