IL-11 Protects Human Microvascular Endothelium from Alloinjury In Vivo by Induction of Survivin Expression

Nancy C. Kirkiles-Smith, Keyvan Mahboubi, Janet Plescica, Jennifer M. McNiff, James Karras, Jeffrey S. Schechner, Dario C. Altieri and Jordan S. Pober

*J Immunol* 2004; 172:1391-1396; doi: 10.4049/jimmunol.172.3.1391
http://www.jimmunol.org/content/172/3/1391

**Why The JI?**

- **Rapid Reviews! 30 days** from submission to initial decision
- **No Triage!** Every submission reviewed by practicing scientists
- **Speedy Publication!** 4 weeks from acceptance to publication

*average

**References**

This article cites 40 articles, 13 of which you can access for free at:
http://www.jimmunol.org/content/172/3/1391.full#ref-list-1

**Subscription**

Information about subscribing to *The Journal of Immunology* is online at:
http://jimmunol.org/subscription

**Permissions**

Submit copyright permission requests at:
http://www.aai.org/About/Publications/JI/copyright.html

**Email Alerts**

Receive free email-alerts when new articles cite this article. Sign up at:
http://jimmunol.org/alerts
IL-11 Protects Human Microvascular Endothelium from Alloinjury In Vivo by Induction of Survivin Expression

Nancy C. Kirkiles-Smith,*† Keyvan Mahboubi,*† Janet Plescia,2*‡ Jennifer M. McNiff,‡ James Karras,§ Jeffrey S. Schechner,*† Dario C. Altieri,2*† and Jordan S. Pober3*†‡

IL-11 can reduce tissue injury in animal models of inflammation but the mechanism(s) is unknown. When C.B-17 SCID/beige mice bearing human skin grafts are injected i.p. with human PBMC allogeneic to the donor skin, infiltrating T cells destroy human microvessels by day 21. Intradermal injection of human IL-11 (500 ng/day) delays the time course of graft microvessel loss without reducing the extent of T cell infiltration. Protective actions of IL-11 are most pronounced on day 15. IL-11 has no effect on T cell activation marker, effector molecule, cytokine expression, or endothelial ICAM-1 expression. IL-11 up-regulates the expression of survivin, a cytoprotective protein, in graft keratinocytes and endothelial cells. Topical application of survivin antisense oligonucleotide down-regulates survivin expression in both cell types and largely abrogates the protective effect of IL-11. We conclude that in this human transplant model, IL-11 exerts a cytoprotective rather than anti-inflammatory or immunomodulatory effect mediated through induction of survivin. The Journal of Immunology, 2004, 172: 1391–1396.

Microvascular endothelial cells (EC)4 in vascularized allografts are primary targets of acute allogeneic rejection responses (1–3). Our laboratory has developed a novel human PBL-SCID/human skin allograft model that allows for examination of human T cell interactions with human dermal microvessels in an immunodeficient mouse host (4). In this model, the graft EC become activated, expressing adhesion molecules such as ICAM-1 and VCAM-1, after which circulating human CD3+ T cells infiltrate the grafts and cause endothelial cell injury (4) reminiscent of human first-set skin rejection (1). This process can be inhibited with immunosuppressive drugs (5) or human costimulator blockade (6), supporting the interpretation that this model represents a human rejection reaction.

IL-11 is a pleiotropic cytokine that shows anti-inflammatory, immunomodulatory, and cytoprotective effects (7). IL-11 decreases injury in a number of animal models of acute and chronic inflammation (8–12). Daily intradermal (i.d.) injections of IL-11 also reduce injury and inflammation in human psoriatic skin lesions (13). We have previously demonstrated that low-dose IL-11 can inhibit T cell-mediated injury in cultured EC but had no effects on EC inflammatory responses such as TNF-induced adhesion molecule expression (14). The protective effect is dependent on new protein synthesis, consistent with the idea that IL-11 induces expression of a cytoprotective protein, and we have demonstrated that IL-11 causes induction of survivin, an inhibitor of apoptosis (IAP) family member, in cultured EC (15). There are no observations linking survivin expression to resistance to T cell-mediated injury. It has proven difficult to link any candidate protective proteins induced in cultured EC to cytoprotection because these cells depend upon the presence of growth factors for survival in vitro, and growth factors act, in part, by up-regulating multiple antiapoptotic genes, including survivin. Thus, we could only examine the response to IL-11 in cultured cells about to undergo apoptosis due to growth factor withdrawal. For this reason, it is actually easier to dissect the cytoprotective mechanism of action of IL-11 in vivo using our SCID mouse skin graft model. Our previous studies have shown that in human skin xenografts, i.d. injected IL-11 induces survivin expression in both keratinocytes and dermal microvascular EC (15). The objectives of the current study were to determine whether IL-11 could protect endothelium from T cell-mediated damage in vivo and, if so, could we attribute this effect to induction of survivin. These studies confirm that IL-11 provides significant but incomplete protection of the microvasculature from T cell-mediated allograft rejection without reduction in inflammation or evidence of immunomodulation. Moreover, down-regulation of survivin expression by means of topical antisense oligonucleotide confirms a role for survivin in IL-11-induced cytoprotection.

Materials and Methods

Animals

C.B-17 SCID/beige mice (Taconic Farms, Germantown, NY) were used at 5–8 wk of age. The animals were housed individually in microisolator cages and were fed autoclaved food and water. Serum IgG levels were determined by sandwich ELISA using reagents from Cappel (Durham, NC) as previously described (16). SCID/beige animals were considered “leaky” at IgG levels >1 μg/ml and excluded from experimental use.

Skin grafting

Human skin was obtained from cadaver donors through the Yale University Skin Bank under a protocol approved by the Yale Human Investigations Committee. Human skin was orthotopically transplanted to SCID/beige mice as previously described (16, 17). This and all subsequent
experiments were performed under a protocol approved by the Yale Animal Care and Use Committee. In brief, 0.5-mm-thick sheets were divided into 1-cm² pieces and fixed onto similar sized defects on the dorsum of recipients using staples. The resultant surface area of healed grafts was kept constant between animals when possible. The skin reproduced correctly was assayed for revascularization rate and was allowed to heal for 4 wk before an injection of allogeneic (to the skin) human PBMC or graft treatment. Rare animals that did not successfully engraft were excluded from the experimental groups before treatments.

**PBMC isolation and administration**

Human leukocytes were collected by leukapheresis of adult volunteer donors under a protocol approved by the Yale Human Investigations Committee. The PBMC were isolated using Lymphocyte Separation Medium (Cappel) according to the manufacturer’s instructions. The cells were stored in 10% DMEM/90% FBS at −196°C and were thawed and washed before use. Thawed leukocytes typically contain ~73% CD3⁺ T cells, 5% CD16⁻ macrophages, 9% CD19⁺ B cells, 14% CD56⁻ NK cells, and equally divided between CD45RA⁻ and CD45RO⁻ cells (18). SCID/beige mice were reconstituted with 3 × 10⁶ human PBMC by i.p. inoculation 4 wk after skin engraftment. The number of circulating human T cells was determined daily for 4 wk using CD3-fluorescein isothiocyanate (FITC), CD4-fluorescein isothiocyanate (FITC), and CD8-fluorescein isothiocyanate (FITC) mAbs and were analyzed using a FACSort (BD Biosciences, Mountain View, CA). A discrete population of circulating human T cells, with a frequency of >0.5% of mouse leukocytes, was detected in >95% of recipients. The average reconstitution percentage was 5.28 ± 0.195. Animals demonstrated no signs of graft-vs-host disease. Rare animals that failed to reconstitute with human T cells were, by prior design, excluded from analysis. None of the treatments used in this study influenced the frequency or extent of T cell engraftment.

**Graft treatments**

Recombinant human IL-11 (gift from Wyeth, Cambridge, MA) was diluted in pyrogen-free saline to a dose of 500 ng in 20 µl and administered directly into the grafts by i.d. injection using a 29-gauge tuberculin syringe. Daily IL-11 or pyrogen-free saline treatment was initiated 4–5 wk after skin grafting and 1 day before PBMC injection. Skin was harvested at the specified time points.

Antisense oligonucleotide (ASO) creams, prepared by ISIS Pharmaceuticals (Carlsbad, CA), were used to down-regulate survivin expression in skin grafts. Irrelevant and survivin ASO (ISIS 23722 and ISIS 28598, respectively) creams were applied topically (100 µl three times/day) to skin grafts between days 5 and 10 after BMC inoculation. Efficacy and specificity of creams on survivin expression was assessed by immunohistochemistry using paraffin-embedded sections or by real-time quantitative RT-PCR (see below).

**Histology and immunohistochemistry**

Human skin grafts, harvested at indicated times, were processed for paraffin-embedded or frozen sections as previously described (17). Immunostaining was performed (17) using isotype-matched, nonbinding control Abs or the following Abs: mouse anti-human CD3 (UCHT1, IgG1), mouse anti-human ICAM-1 (BD5), or mouse anti-human CD31 (platelet-endothelial cell adhesion molecule-1 (PECAM-1); DAKO, Carpinteria, CA). Survivin immunostaining was performed on paraffin-embedded sections as previously described (15) using rabbit anti-survivin (Novus Biologicals, Littleton, CO) or rabbit IgG control.

The degree of graft microvascular damage was evaluated from HE-stained sections by a dermatopathologist (J.M.M.) blinded to treatment protocols as previously described (6). In brief, the percentage of dermal vessels showing injury, defined as EC loss or sloughing, was assessed from an average of three high-power (×200) fields using the following semiquantitative grading scale: grade 0, all vessels patent and uninvolved; grade 1, <25% of vessels show injury; grade 2, 50% of vessels show injury; and grade 3, >75% of vessels show injury. The number of human microvessels in the dermis of human skin grafts was quantified by counting vessels whose EC stained positively for human CD31. A minimum of three fields was counted for each graft. The staining intensity and distribution of human ICAM-1 on EC was evaluated in a blinded fashion by N.C.K.-S. and K.M. as previously described (17). In brief, Ag immunostaining from an average of three high-power (×200) microscopic fields was assessed using the following semiquantitative grading scale: grade 0, absent or faint staining of an occasional vessel only; grade 1, faint staining of several vessels; grade 2, moderate staining of most vessels; and grade 3, intense staining of most vessels. The staining intensity and distribution of human CD3⁺ T cell infiltrates were similarly scored using the following semiquantitative grading scale: grade 0, none or occasional positive cells only; grade 1, sparse infiltration of positive cells; grade 2, moderate infiltration of positive cells; and grade 3, intense positive staining infiltrates. Where indicated, the actual numbers of CD3⁺ T cells per five high-powered fields were enumerated by two independent observers (N.C.K.-S. and K.M.) blinded to the treatment protocol.

**Quantitative real-time PCR**

Quantitative real-time PCR were performed as previously described (19, 20) on skin grafts harvested 15 days after PBMC inoculation. Briefly, cDNA was amplified by AmpliTaq Gold DNA polymerase using specific primers which were synthesized by Yale Howard Hughes Medical Institute/Kecskeméti oligonucleotide synthetic facility (Yale University School of Medicine, New Haven, CT): CD3e (5’-GGCAAAGGGGCAAAACAAAG-3’ and 5’-CTTCCGGATGGGCTCATAG-3’), Fas ligand (5’-GGCCCCATTTTAAAGGAAATGGT-3’ and 5’-CAGGACATTCTCATGTTCTTC-3’), granzyme B (5’-TGTCGACCACTGGCTCTC-3’ and 5’-CCGATGTACCTCTCCTCATG-3’), perforin (5’-TGGAGTGGCCGCTTACATAGT-3’ and 5’-GTGGTGTCGTAGTGGAAGAT-3’), IL-4 (5’-AGCCCAAGCTCCATTCTG-3’ and 5’-TCCAAGGCCAGTGACATTGGA-3’), GAPDH (5’-GAAGACTGGAAGTGCGGATC3’ and 5’-GAAGATGTGGTGGAGTTTCC3’), suppressor of cytokine signaling-3 (SOCS-3) (5’-GCGGACTCTTCACTACATC-3’ and 5’-ATCGTACTGTGCTAGGAACC3’), and survivin (5’-GCCACTCTACGGGTTTAT-3’ and 5’-CTCCTGTCGGACATCAAGA-3’). IL-5, IFN-γ, ICAM-1, and ICAM-2 were determined at baseline and at days 5 and 10 using a primer/probe set from Applied Biosystems (Applied Biosystems of Perkin-Elmer; Foster City, CA). The reaction was amplified with an iCycler iQ Multicolor Real-Time Detection System (Bio-Rad, Hercules, CA).

Changes in the levels of mRNA were measured by the cycle threshold (C_T), i.e., the PCR cycle at which an increase in reporter fluorescence can be first detected above a baseline signal. C_T values for GAPDH, ICAM-2, or CD3e cDNA were subtracted from C_T values for appropriate cDNA for each well to calculate ΔC_T. The triple-triplicate ΔC_T values for each sample were averaged. The averaged ΔC_T values calculated for control grafts was subtracted from ΔC_T values calculated for IL-11-treated grafts to calculate ΔΔC_T. Then, the fold induction for each well was calculated by using the 2^(ΔΔC_T) formula. The fold induction value for triplicate wells was averaged and data are presented as the mean ± SEM of triplicate wells.

**Data analysis**

Scores of histologic data, quantities of EC or T cells, or normalized mRNA levels were pooled from several experiments. For each parameter, results are expressed as the mean ± SD. Experiments only using grafts receiving PBMC were compared using a paired t test. The effects of IL-11 vs saline and the effects of survivin ASO vs control oligonucleotide were analyzed using a one-way ANOVA followed by a Bonferroni correction. Differences between groups are considered as significant when p < 0.05.

**Results**

**Intradermal administration of IL-11 into human skin grafts delays the time course of allograft injury in vivo**

To investigate the effects of IL-11 on immune-mediated alterations in human skin grafts, daily i.d. injections of IL-11 or saline vehicle were administered to groups of animals with healed human skin grafts starting on the day before i.p. inoculation with PBMC. Within each experiment, all skin grafts were obtained from a single skin donor and All PBMC came from a second donor allogeneic to the skin graft donor. In each experiment, additional control animals bearing skin grafts were injected with IL-11 or saline but were not inoculated with PBMC.

First, we examined the time course of IL-11 effects. Since destruction of human microvessels is not seen before 7 days and is usually complete by 21 days after PBMC inoculation, we examined grafts on days 10, 15, and 21. The number of human CD3⁺ T cell profiles was unchanged in animals not receiving PBMC at all time points examined. There were no discernable effects of i.d. IL-11 on the numbers of circulating human T cells (data not
IL-11-treated grafts at day 15 compared with saline controls, but the difference from saline-treated animals narrowed by day 21 (Fig. 1B). IL-11 treatment had no effect on the extent of graft infiltration by CD3⁺ T cells at any time point examined (Fig. 1C). Thus, the administration of exogenous IL-11 delays the time course of rejection of skin allografts without a concomitant decrease in lymphocytic infiltration.

IL-11 does not exert an anti-inflammatory or immunomodulatory effect at day 15 after PBMC inoculation

To further investigate the mechanisms of IL-11 actions, we focused our subsequent experiments on day 15 specimens, i.e., the time when the effect of IL-11 was most clearly evident. Consistent with the time course experiments, IL-11 did not change T cell numbers in the grafts (Table I). It also did not affect the level of transcripts encoding IFN-γ, IL-5, perforin, granzyme B, CD69, or CD25 (Table II).

Similarly, ICAM-1 induced on microvessel EC was not reduced as detected by immunostaining (Fig. 2). Cumulatively, these data argue against either an anti-inflammatory effect or an immunomodulatory effect and support cytoprotection as the primary mechanism of IL-11-mediated reduction of EC injury in our model.

IL-11 induces survivin expression in human skin grafts

Because previous studies have shown that IL-11 causes induction of survivin in both microvascular EC and keratinocytes of human skin grafts, we focused on this protein. In the current studies, IL-11 induced survivin expression in both the control (no PBMC) and PBMC-infiltrated human skin grafts (Fig. 2, G and I). In grafts receiving PBMC alone but not IL-11, there was no induction of survivin expression over baseline (Fig. 2, G and I). Data pooled from multiple experiments are summarized in Fig. 2J.

Topical administration of survivin ASO cream down-regulates survivin expression and abrogates the IL-11-induced cytoprotection in human skin grafts

To examine whether survivin plays a role in IL-11-mediated protection, we inhibited survivin expression through the use of topical application of survivin ASO creams. To confirm that the survivin ASO cream was effective and specific in down-regulating survivin expression, we quantified the effects of IL-11 on survivin and SOCS-3 mRNA expression in skin grafts receiving either control or survivin ASO cream. SOCS-3 was examined because it is also induced by IL-11 in cultured EC (18). Survivin ASO cream appears specific for survivin as topical application of survivin ASO cream abrogated survivin expression (Fig. 3A) but not SOCS-3 induction (Fig. 3B) in response to i.d. inoculation of 500 ng IL-11.

Finally, we examined the effects of selectively reducing survivin expression in IL-11-induced graft cytoprotection by applying antisense creams thrice daily between days 5 and 10 after PBMC inoculation. While the protective effect of IL-11 was abrogated by survivin ASO, this reduction in expression did not abrogate the IL-11-induced increase in SOCS-3 expression (Fig. 3B), nor was it sufficient to induce CD3⁺ T cell infiltration (Fig. 1C).

Table I. Effects of IL-11 on injury and inflammation in human skin grafts

<table>
<thead>
<tr>
<th>IL-11 (ng)</th>
<th>No. of Skin Grafts</th>
<th>No. of Human Vessels/Graft</th>
<th>Endothelial Injury</th>
<th>Human CD3⁺ Infiltration</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>16</td>
<td>–</td>
<td>92.6 ± 6.8</td>
<td>0 ± 0</td>
</tr>
<tr>
<td>500</td>
<td>17</td>
<td>–</td>
<td>103 ± 2.0</td>
<td>0 ± 0</td>
</tr>
<tr>
<td>0</td>
<td>18</td>
<td>+</td>
<td>51.5 ± 2.1</td>
<td>2.4 ± 0.06</td>
</tr>
<tr>
<td>500</td>
<td>18</td>
<td>+</td>
<td>98.4 ± 1.6</td>
<td>0.93 ± 0.05*</td>
</tr>
</tbody>
</table>

* Human skin was engrafted onto SCID/beige mice, which were either not reconstituted or inoculated with 3 × 10⁸ human PBMC i.p. Skin grafts were then treated with IL-11 (500 ng/day) or saline i.d. every day until harvest at day 15. Data represent mean values ± SD. Cytokine-treated groups were compared to untreated groups. Statistical significance was determined using a one-way ANOVA followed by a Bonferroni test.

* * p < 0.05.
inoculation. This dosing strategy, developed through pilot experiments, effectively inhibits survivin expression after daily IL-11 injections assessed on day 15 by immunohistochemistry (Fig. 3, C–F). Counts of retained human microvessels show that IL-11-mediated protection of human vessels at day 15 compared with saline treatment is not reduced by application of irrelevant ASO cream groups (Fig. 3G). When survivin is inhibited with specific ASO, endothelial injury in the IL-11-treated grafts becomes as extensive as that in saline-treated control animals (Fig. 3H). Taken together, these data suggest a role for survivin in IL-11-induced protection of graft endothelium.

Discussion

In the current study, we have shown that IL-11, a pleiotropic member of the IL-6 cytokine family, exerts a cytoprotective effect in a model of human T cell-mediated allograft rejection. More specifically, this response depends on the induction of survivin in graft EC.

IL-11 has previously been shown to reduce tissue damage in several animal models (9–12, 21) as well as in human psoriatic skin (13). The mechanism(s) of these effects is not known. One hypothesis has been that IL-11 exerts anti-inflammatory effects. In

<p>| Table II. Effects of IL-11 on cytokine and cytolytic effector molecules in human skin grafts a |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>No. of Human Vessels/Graft</th>
<th>IFN-γ</th>
<th>IL-5</th>
<th>Perforin</th>
<th>Granzyme B</th>
<th>Fas Ligand</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline</td>
<td>76 ± 3.49</td>
<td>35.5 ± 1.28</td>
<td>453.8 ± 102</td>
<td>10.91 ± 0.51</td>
<td>1.01 ± 0.083</td>
</tr>
<tr>
<td>IL-11</td>
<td>133.8 ± 7.19*</td>
<td>20.4 ± 1.72</td>
<td>358.15 ± 52</td>
<td>14.98 ± 0.90</td>
<td>1.14 ± 0.058</td>
</tr>
</tbody>
</table>

* Human skin was engrafted onto SCID/beige mice, which were reconstituted with $3 \times 10^8$ human PBMC i.p. Skin grafts were then treated with IL-11 (500 ng/day; $n = 6$) or saline ($n = 6$) i.d. every day until harvest at day 15. Data represent mean values ± SD. Cytokine-treated groups were compared to untreated groups. Statistical significance was determined using a paired $t$ test. $*, p < 0.05.$

**FIGURE 2.** Immunocytochemical assessment of ICAM-1 induction. Skin grafts were harvested 15 days after i.p. injection of PBMC. A, Saline (i.d.), no PBMC; B, daily i.d. injections of 500 ng IL-11, no PBMC; C, saline (i.d.) with PBMC; D, daily i.d. injections of 500 ng IL-11 with PBMC; E, quantification of ICAM-1 scoring. IL-11 treatment does not reduce the induction of ICAM-1 expression. Immunocytochemical assessment of survivin expression in keratinocytes and vascular endothelium. Human skin grafts harvested 15 days after i.p. injection of allogeneic PBMC. F, Saline (i.d.), no PBMC; G, daily i.d. injections of 500 ng IL-11, no PBMC; H, saline (i.d.) with PBMC; I, daily i.d. injections of 500 ng IL-11 with PBMC; J, quantification of survivin staining intensity. IL-11 induces survivin expression, while infiltrating T cells do not influence this response.
support of this role, it has been shown that IL-11 can inhibit NF-κB expression in a murine macrophage cell line (22). Another idea has been that IL-11 is immunomodulatory, causing harmful Th1-type responses to change into less injurious Th2-type responses (23–25). In our human skin graft model, we failed to observe either a reduction in T cell infiltration or a change in cytokines, effector molecules, or T cell activation markers. Thus, our data tend to favor a third idea, namely, that IL-11 can increase the capacity of EC and other cell types to resist injury. We first noted this effect in cultured EC (12, 14) and, based on the results of our ASO experiments, attributes this effect largely to the enhanced expression of survivin.

Survivin is the simplest member of the apoptosis protein (IAP) family, containing a single baculovirus inhibitory repeat domain (26). IAP family members, including survivin, are believed to act as caspase inhibitors (27). Survivin also appears to associate with the mitotic spindle and influence cytokinesis. Survivin is widely expressed in development but is largely shut off in the adult. It is re-expressed in most common tumors and angiogenic endothelium (28–30). Knockdown of survivin expression sensitizes cells to apoptosis (31–34). Our model is the first example of survivin protecting target cells from T cell-mediated injury.

The factors that regulate survivin appearance in adult tissues are not well known. In cultured EC, survivin can be up-regulated by growth factors and related agents (e.g., vascular endothelial growth factor or angiopoietin) through activation of phosphatidylinositol 3-kinase and Akt (30, 35). IL-11 does not activate this pathway yet effectively induces survivin expression (15). Previous cultured cell experiments in our laboratory have linked both survivin expression and resistance to injury to STAT3 signaling (15).

The cytoprotective effects of IL-11 in vivo are reminiscent of the phenomenon of accommodation. Originally described as an explanation for the survival of ABO incompatible allografts in the face of circulating alloantibodies (36–38), Bach and colleagues (39, 40) have extended this concept to describe the capacity of both allografts and xenografts to survive in nontolerant hosts capable of cell-mediated as well as humoral rejection. The accommodated state is associated with increased expression of several antiapoptotic genes in graft EC, including A20, Bcl-2 family members (Bcl-2, Bcl-xL, A1), and heme oxygenase-1 (HO-1) (38). HO-1, in particular, has been shown to be important in the accommodation of mouse cardiac allografts by comparing organs from wild-type and HO-1 knockout animals (41). We have not observed a consistent effect of IL-11 on HO-1 expression, nor have we seen effects of IL-11 on A20 or Bcl-2 family members (K.M. and J.S.P., unpublished observations). Survivin has not previously been linked to accommodation, but nor has it been specifically excluded.

In summary, the in vivo experiments in human tissue reported here extend and confirm previous in vitro studies examining the
role of IL-11 in protecting the vascular endothelium from T cell-mediated injury. Although IL-11 does not completely prevent allograft rejection, it reproducibly delays the time course of vessel loss. The mechanism by which IL-11 protects EC can be explained in large part by graft accommodation mediated by the induction of survivin expression and not via an anti-inflammatory or immunomodulatory effect. Indeed, there appears to be no effect of IL-11 on the number of T cells, their activation state, their pattern of cytokine synthesis, or effector molecule synthesis in our model. These findings do not exclude the possibility that additional cytoprotective genes induced by IL-11 also contribute to reduced injury. However, this study provides the first evidence that survivin can protect cells from T cell-mediated injury. Our findings may be valuable in optimizing the applications of IL-11 as a protective agent in human patients.

Acknowledgments

We thank Bruce Fichandler for providing cadaveric skin and Lisa Gras and Louise Bensen for their expert technical assistance.

References

8. Tereb, D. A., N. C. Kirkiles-Smith, R. W. Kim, D. Bungard, and J. L. Ferrara. 1998. Interleukin-11 promotes T cell polarization and activates human endothelial cells to resist immune-mediated injury. Our findings do not exclude the possibility that additional cytoprotective genes induced by IL-11 also contribute to reduced injury. However, this study provides the first evidence that survivin can protect cells from T cell-mediated injury. Our findings may be valuable in optimizing the applications of IL-11 as a protective agent in human patients.

Acknowledgments

We thank Bruce Fichandler for providing cadaveric skin and Lisa Gras and Louise Bensen for their expert technical assistance.

References

8. Tereb, D. A., N. C. Kirkiles-Smith, R. W. Kim, D. Bungard, and J. L. Ferrara. 1998. Interleukin-11 promotes T cell polarization and activates human endothelial cells to resist immune-mediated injury. Our findings do not exclude the possibility that additional cytoprotective genes induced by IL-11 also contribute to reduced injury. However, this study provides the first evidence that survivin can protect cells from T cell-mediated injury. Our findings may be valuable in optimizing the applications of IL-11 as a protective agent in human patients.

Acknowledgments

We thank Bruce Fichandler for providing cadaveric skin and Lisa Gras and Louise Bensen for their expert technical assistance.

References