

Volume 12, issue 1, March 2001 | Articles originaux

Development of allergic contact dermatitis requires activation of both tumor necrosis factor-receptors.

Abstract

We investigated the role of the TNF receptors, type I (p55TNFR) and type II (p75TNFR), in a mouse model of contact hypersensitivity i.e., a model of a delayed type hypersensitivity (DTH) allergic reaction. Mice deficient for p55TNFR or p75TNFR were used to investigate the functions of these receptors in development of the DTH reaction. We show that both TNF receptors have a strong influence on the overall outcome of the DTH reaction, with the two TNF receptors exerting distinct functions. Dendritic cells of mice lacking p55TNFR

had a defect in allergen uptake but showed normal migration into regional lymph nodes. In contrast, dendritic cells of p75TNFR-deficient mice showed diminished migration into regional lymph nodes after allergen contact, whereas the allergen uptake was independent of the p75TNFR. Thus, both TNF receptors are required for the development of a complete DTH reaction.

Full text

INTRODUCTION

Langerhans cells (LC) migrate into peripheral secondary lymphoid organs and present processed antigen *via* MHC-class I and MHC-class II to antigen specific T lymphocytes, leading to antigen-specific activation and polyclonal expansion of the reactive T lymphocytes [1]. Allergen transport from the epidermis into the regional lymph node (LN) is an essential step for successful sensitization in a DTH reaction [2, 3]. LC in the epidermis are specialized in incorporating large amounts of antigen by phagocytosis, pinocytosis, and receptor-mediated endocytosis [4-6]. Migration of LC is dependent on an altered expression of adhesion molecules by the LC [7]. Furthermore, the interaction between the LC and the extracellular matrix changes, enables LC migration to secondary lymphoid tissues [8]. Shortly after allergen contact, LC begin to migrate from the epidermis to regional LN, accompanied by maturation of the LC [9, 10]. The cytokine and chemokine milieu of the dermis and later of the LN, changes after allergen contact. LC belong to the family of dendritic cells (DC). In the epidermis DC and keratinocytes are thought to be responsible for the production of TNF and IL-1. Both cytokines administered locally or systemically are able to induce migration of LC/DC out of the epidermis into secondary lymphoid organs [11]. TNF exerts its activity *via* two distinct receptors with an apparent molecular weight of 55 kD (p55TNFR) and 75 kD (p75TNFR), respectively. TNF is thought to play an important role in the sensitization and the elicitation phase of the DTH reaction [12, 13].

In this study, we investigated the role of p55TNFR and p75TNFR in the transport of the contact allergen from the site of exposure into the draining LN. For this purpose we used mice deficient in either the p55TNFR or the p75TNFR. We show that both TNF receptors influence the outcome of the contact hypersensitivity (CHS) reaction, a model of DTH, by distinct mechanisms. The p55TNFR-deficient mice showed a strongly reduced response to contact allergen and displayed a

severe defect in allergen transport from the site of exposure to the regional LN, caused by defective uptake of allergen by DC of the epidermis. The p75TNFR-deficient mice showed a less severe reduction of the CHS response to contact allergen. We found that the p75TNFR had a strong influence on the migration of DC from the epidermis to the regional LN. In our model, development of CHS is clearly dependent on the expression of both the p55TNFR and the p75TNFR, both playing distinct roles during the sensitization phase of DTH.

METHODS

Animals

Wild type (wt) mice, strain C57BL/6, were obtained from Charles River (Sulzfeld, Germany). Mice deficient in the p55TNFR (p55TNFR k.o.), kindly provided by K. Pfeffer [14] (Munich, Germany), and p75TNFR-deficient mice (p75TNFR k.o.), kindly provided by H. Bluethmann [15] (Basel, Swizerland), had been backcrossed six times with mice of strain C57BL/6. Mice used for CHS experiments were age- and sex-matched. All mice were fed with a standard diet and received water *ad libitum.*

Contact hypersensitivity reaction

The abdominal fur was removed with a razor and 125 mul of either 7% TNCB (2-4-6-trinitro-1-chlorbenzol, Applichem, Darmstadt, Germany) solution in acetone:olive oil (4:1) or 3% oxazalone (4-ethoximethylene-2-phenyloxazol-one, Sigma, St. Louis, MO, USA) solution in ethanol:acetone (3:1) were applied to the skin and allowed to dry. Five (oxazalone) to 6 (TNCB) days later mice were challenged on the dorsal and ventral surface of the pinnae with 20 mul of 1% TNCB (4:1 acetone:olive oil) or 3% oxazalone (ethanol:acetone). The increase in thickness of the pinnae was measured with a spring-loaded micrometer (Oditest S-5010, Kroeplin, Schlüchtern, Germany) before challenge and at various time points up to 120 hours after challenge. The results represent the mean increase at the indicated time-points after challenge of at least 5 animals per group.

Assay for hapten-induced DC migration

The abdominal fur was removed with a razor and 400 mul of 0.5% FITC (fluorescein 5-isocyanate, Sigma, St. Louis, MO, USA) solution in

acetone:dibutylphthalate (1:1) (Fluka, Buchs, Germany) were applied to the skin and allowed to dry. Twenty-four hours later axillary and inguinal LN were collected. The LN were gently disrupted and the stroma was digested with collagenase IV (Sigma, St. Louise, MO, USA) (0.4 mg/ml) and DNase I (Sigma, St. Louis, MO, USA) (0.02 mg/ml) solution at room temperature for 30 min and then filtered through a nylon mesh (pore size 100 mum). DC were enriched by a density centrifugation step on a metrimazide gradient (Sigma, St. Louis, Mo, USA). Filtered cells were resuspended in DMEM with 1% FCS and layered on 14.5% metrimazide at a concentration of 1-5 x 10^6 cells/ml and centrifuged at 800 g for 15 min. Cells were collected from the interphase and washed once with PBS containing 1% FCS and resuspended in PBS containing 0.1% FCS. FITC-bearing cells were examined flow-cytometrically with a FACS-Calibur instrument (Beckton Dickinson, Heidelberg, Germany). In order to exclude non-viable particles from measurement, a propidium-iodide (PI) (Sigma, St. Louise, MO, USA) counterstaining (1 mug/ml) was performed. The first (FL-1) and the third (FL-3) channel were used to detect green and red fluorescence of the cells. The autofluorescence of cells, derived from the control group, treated with solvent alone, served as negative control. The results were expressed as cells per LN.

Statistical analysis

The statistical significance of the differences in the means for each experimental group was calculated using Student's *t*-test. Mean differences were considered significant when $p < 0.05$.

RESULTS

The CHS reaction is dependent on the p55TNFR and the p75TNFR

Both, the p55TNFR and the p75TNFR, are necessary for a complete CHS reaction. Wt mice showed a specific allergic reaction toward TNCB and oxazalone (Figures 1, 2). TNCB: wt: 0.32 ± 0.05 mm; wt control group: 0.12 ± 0.04 mm (Figure 1); oxazalone: wt: 0.27 ± 0.05 mm; wt control group: 0.05 ± 0.04 mm) (Figure 2). In the case of TNCB (Figure 1), the p55TNFR-deficient mice did not exhibit any allergic reaction (0.11 ± 0.03 mm; p55TNFR-deficient control mice: 0,06 ± 0,03 mm). In the case of oxazalone (Figure 2), the p55TNFR-deficient mice showed a strongly reduced CHS reaction (0.16 ± 0.03 mm) compared to wt mice ($p < 0.01$), but a significantly stronger reaction than mice of the control

groups (p55TNFR-deficient mice: 0.04 ± 0.02 mm, $p < 0.01$; wt control group: $p < 0.01$). Mice deficient in the p75TNFR developed a significantly reduced allergic CHS to TNCB (Figure 1) (0.18 ± 0.07 mm) and oxazalone (Figure 2) (0.21 ± 0.03 mm) compared to wt mice (TNCB/oxazalone $p < 0.01$; TNCB: wt control mice: $p < 0.01$). Control mice challenged, but not sensitized did not show any allergic reaction (Figures 1, 2) (Figure:1; p75TNFR-deficient mice: 0.04 ± 0.02 mm, Figure 2; oxazalone: p75TNFR-deficient mice: 0.02 ± 0.02 mm).

Both TNF receptors influence antigen transport

To determine the migration of LC from the skin into regional LN we used FITC as a contact allergen. Cells that had migrated into the regional LN (axillary and inguinal) after allergen application were counted flow-cytometrically (Figure 3). The p55TNFR had no influence on the migration of LC since no significant difference was found between the total number of migrated cells in wt mice (66,000 cells/LN) and mice deficient in the p55TNFR (68,000 cells/LN). However, we found about a 50% decrease in FITC-bearing cells in the p75TNFR-deficient mice (37,000 cells/LN) ($p < 0.01$).

To determine the amount of antigen transported into regional LN by DC, we used the same experimental setup. The amount of antigen transported by every cell was determined flow-cytometrically (Figure 4) and calculated within the marker region M1. DC from mice deficient in the p55TNFR transported significantly less antigen per analyzed cell into the regional LN compared to DC from mice positive for the p55TNFR. In contrast, p75TNFR-deficient mice transported more antigen per migrated DC into the regional LN than DC from wild type or p55TNFR-deficient mice (mean fluorescence: wt: 150; p75TNFR-deficient: 210; p55TNFR-deficient: 40).

DISCUSSION

The CHS reaction is a model of DTH of the skin. It is a T cell-dependent allergic reaction that can be divided into a sensitization and an elicitation phase. During the sensitization phase, LC transport contact allergen from the epidermis at sites of first contact into the T cell-rich area of the paracortex of the draining LN, the site of activation and clonal expansion of the allergen-specific T cells. The process of LC migration after contact with allergen is a highly regulated process. LC migration seems to depend on chemokines [16, 17], cytokines [18, 19], and

the expression of adhesion molecules [7, 20]. The proinflammatory cytokine TNF plays an important role in both phases of the DTH reaction, the sensitization phase as well as the elicitation phase. Neutralization of TNF directly before the first contact to allergen or just before allergen challenge prevents the development of CHS [13, 21]. Furthermore, TNF plays a direct role in the migration of LC from the epidermis into draining LN since subcutaneous application of TNF induced the migration of LC from the epidermis [12] whereas neutralization of TNF inhibited the migration of LC into the regional LN [21].

In our experimental model, both TNF receptors influenced CHS independently of the allergen used. The p55TNFR had a stronger influence, because in the TNCB model (Figure 1) we found no CHS in p55TNFR-deficient mice at all and a strongly reduced CHS in the oxazalone model. These results are in contrast to the results presented by Kondo *et al.* [22], describing a CHS reaction independent of the p55TNFR, using DNFB as a contact allergen. In our hands, any attempt to induce a measurable CHS reaction failed using DNFB as a contact allergen (data not shown), although we used mice with the same genetic background (C57Bl/6) as Kondo and coworkers. Since p55TNFR-deficient mice have been shown to lack fully developed germinal centers and follicular dendritic cell networks [23, 24], our finding of impaired CHS in p55TNFR-deficient mice could be due to the disturbed LN microarchitecture which might interfere with antigen presentation.

To better define the roles of the two TNF receptors in the elicitation phase of DTH, we investigated their influence on the amount of antigen transported by the DC from the epidermis into the regional LN. This is a prerequisite for T lymphocyte activation and clonal expansion of allergen-specific clones leading to a successful sensitization. The amount of antigen transported into the regional LN depends on two parameters, the amount of antigen internalized by every cell and the number of cells migrating from the epidermis, the site of allergen contact, to the regional LN. Using FITC as contact allergen and by determining the numbers of DC migrating from the epidermis to the regional LN after allergen contact, we found that the p55TNFR had no influence on the migration of DC from the site of allergen-contact to the regional LN (Figure 3). The same numbers of FITC-positive cells were found in the regional LN of p55TNFR-deficient mice and wt mice, supporting the findings of a previous report [25]. The p75TNFR also influenced CHS in our experiments, in that p75TNFR-deficient mice showed a significant reduction in CHS compared to wt mice in both the TNCB and oxazalone model. These results are in agreement

with those of Wang *et al.* [25] reporting a diminished CHS reaction using oxazalone as a contact allergen in mice with the same genetic background as used in our experiments. The reason for the defective development of DTH in their experiments was explained by an impaired LC migration in FITC-sensitized p75TNFR-deficient mice [25]. Also in our experiments the p75TNFR had a strong influence on the migratory capacity of DC. We found a 50% reduction in the numbers of migrated cells in the p75TNFR-deficient mice (Figure 3).

Isolated DC and DC cultured *in vitro* differentiated equally in respect to their MHC class II antigen, CD40, B7-1 and B7-2 expression, regardless of whether mouse or human TNF, only interact up with the mouse p55TNFR, were used for stimulation (Dr. P. Ricciardi-Castagnoli, Milano, personal communication). In addition, DC from p75TNFR-deficient mice also differentiated morphologically and phenotypically upon stimulation with recombinant murine TNF (Dr. E. Kämpgen, Würzburg, personal communication), indicating that the p75TNFR is not involved in the regulation of DC differentiation. Furthermore, *in vitro* presentation of complete antigen or peptides by DC to specific T cell clones yielded similar stimulation results regardless of whether the DC were derived from wild type, p55TNFR-deficient or p75TNFR-deficient mice (Dr. F. Koch, Innsbruck, personal communication). Concerning the function of the p75TNFR in the sensitization phase of DTH, the defective migration capacity of DC from p75TNFR-deficient mice seems to be the main reason for their failure to develop a normal DTH reaction.

Further analysis of the influence of the TNF receptors on the amount of antigen transported by each DC yielded an additional result. The antigen transport was influenced by the p55TNFR and not by the p75TNFR. The mean fluorescence intensity of migrated DC after FITC sensitization was found to be strongly reduced in cells from p55TNFR-deficient mice compared to cells from wt mice and p75TNFR-deficient mice. This finding could explain the reduced capacity of p55TNFR-deficient mice to develop a complete DTH reaction. The above mentioned observation from preliminary experiments on unimpaired antigen presentation by p55TNFR-deficient DC after *in vitro* exposure to antigen might not fully represent the complete range of antigen uptake and transport events and/or the reaction might be antigen-dependent.

An explanation for this finding can be provided by the different activation mechanisms of the two TNF receptors. The p75TNFR is capable of a p55TNFR-

independent signal transduction and preferentially interacts with membrane-bound TNF which leads to a stronger activation signal of the p75TNFR than soluble TNF [26, 27]. Lucas *et al.* showed that membrane-bound TNF, but not soluble TNF induced the expression of adhesion molecules in p55TNFR-deficient microvascular endothelial cells [28].

CONCLUSION

In this study we have demonstrated that both TNF receptors (p55TNFR and p75TNFR) independently influence the sensitization phase of DTH development. To explain the influence of both TNF receptors on the outcome of the DTH, our data suggest a mechanism by which the p55TNFR influences the antigen uptake by DC, whereas migration of the DC from the epidermis to the draining LN during the sensitization step clearly depends on the p75TNFR.

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Figures

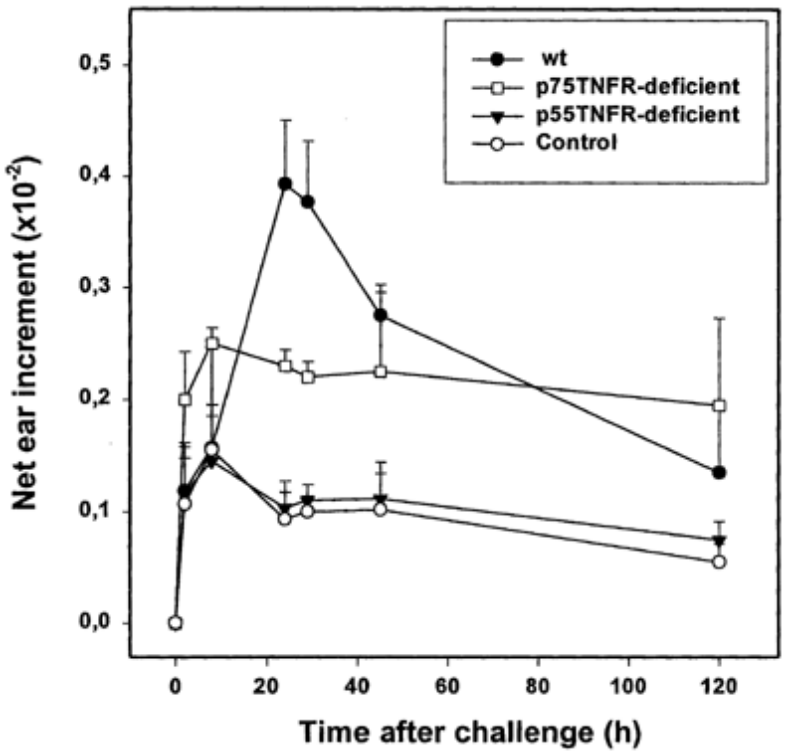


Figure 1

Influence of the TNF receptors on the TNCB-induced CHS reaction.

Mice deficient for the p55TNFR showed no allergic reaction toward TNCB. Mice deficient for the p75TNFR showed a diminished TNCB-induced CHS reaction compared to wt mice. Mice were sensitized with TNCB for six days. The allergic reaction was induced on both pinnae by challenging the mice with TNCB and was quantified by measuring the oedema for a period of 120 hours (mean ± SD). CHS responses were significantly higher in wt and p75TNFR-deficient mice compared to the control groups (* $p < 0.01$), but not in p55TNFR-deficient mice.

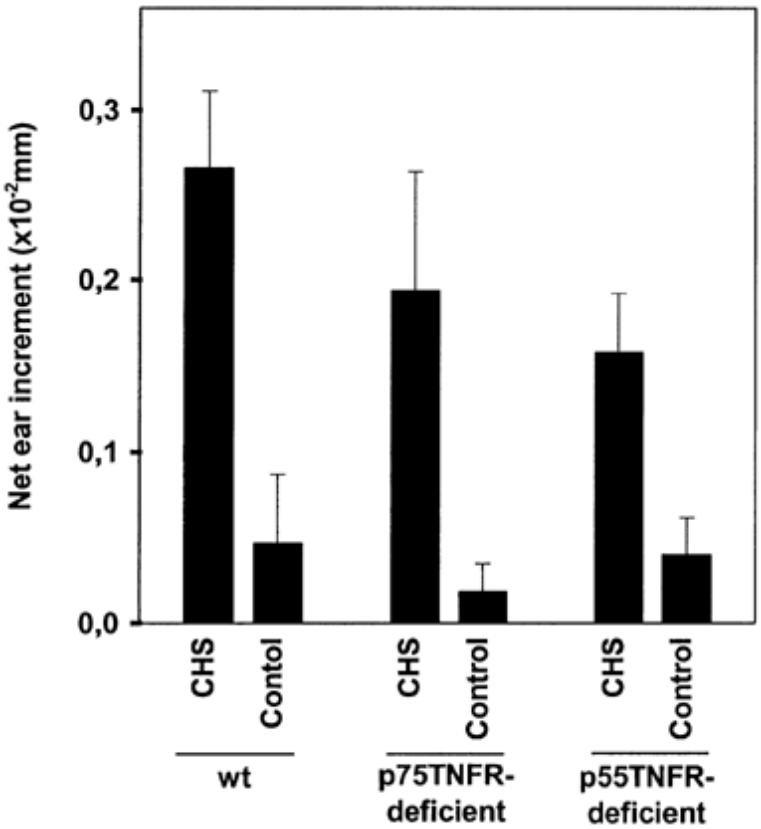


Figure 2

Influence of the TNF receptors on the oxazalone-induced CHS reaction.

Mice deficient for the p55TNFR and the p75TNFR showed a diminished TNCB-induced CHS reaction compared to wt mice. Mice were sensitized for five days with oxazalone. The allergic reaction was induced on both pinnae by challenging the mice with oxazalone and was quantified by measuring the oedema 24 hours later (mean ± SD). The CHS reactions of wt, p75TNFR- and p55TNFR-deficient mice were significantly higher than in the control groups (* $p < 0.01$).

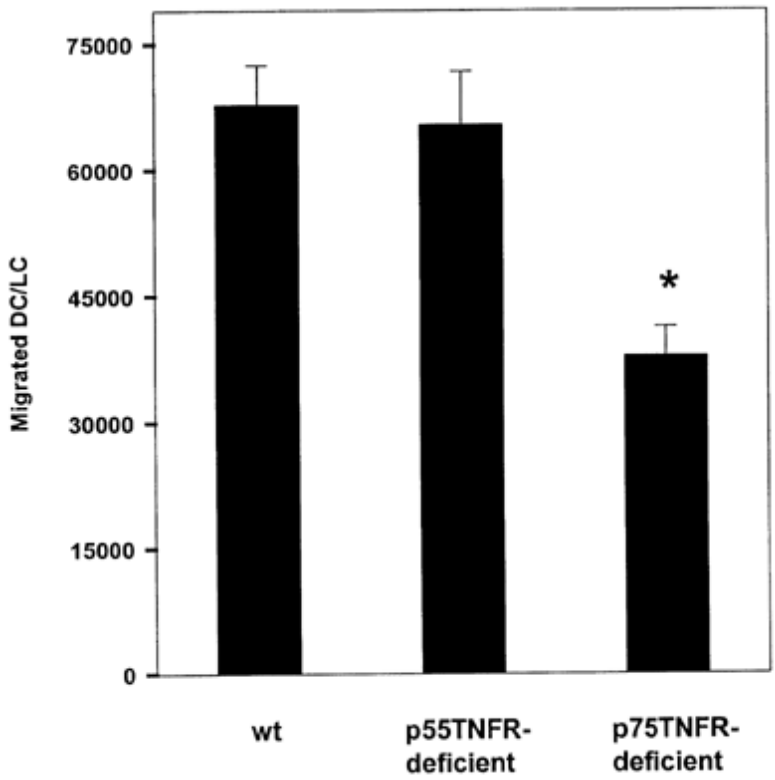
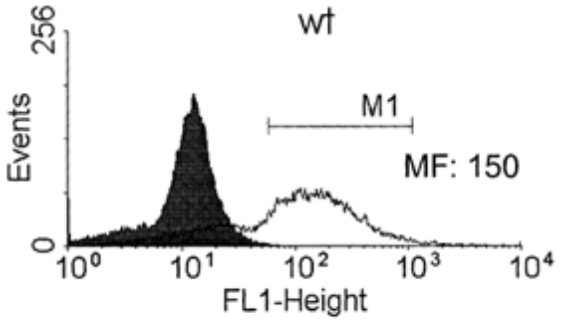
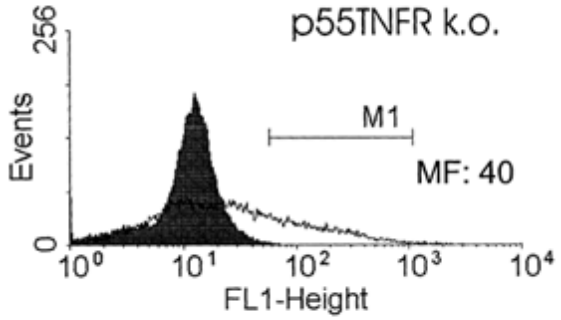

75000
60000
45000
30000
15000
0
Migrated DC/LC
*
wt
p55TNFR-deficient
p75TNFR-deficient

Figure 3

Migration of epidermal DC depends on the p75TNFR.

The p75TNFR triggers migration of DC from the skin into regional LN after contact sensitization. Mice were sensitized with FITC at the abdominal skin and 24 hours later FITC-bearing DC in regional LN were counted flow-cytometrically. Mice treated with solvent alone were used as controls (not shown). For each experiment, cells within the marker region M1 were defined as FITC-positive cells. Significantly lower numbers of FITC-bearing cells migrated from the skin into regional LN in p75TNFR-deficient (p75TNFR k.o.) mice compared to wt or p55TNFR-deficient (p55TNFR k.o.) mice (* $p < 0,01$). The p55TNFR had no influence on the migration of DC since no difference in migrated cell numbers was seen between wt and p55TNFR-deficient mice. One representative experiment out of three independent experiments is shown.





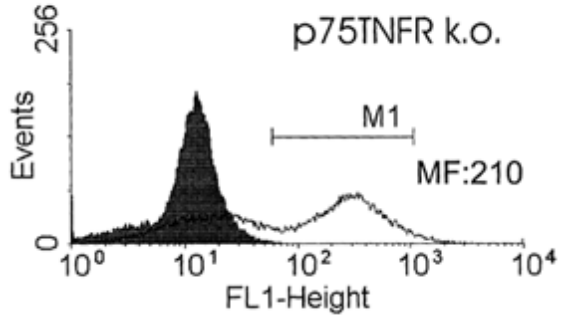


Figure 4

Allergen uptake by epidermal DC depends on the p55TNFR.

Allergen uptake by DC was flow-cytometrically evaluated for wt (A), p55TNFR-deficient (B) and p75TNFR-deficient (C) mice. Animals were painted with FITC on the abdomen, and regional LN cells were collected 24 hours later. DC from p55TNFR-deficient mice (B) transported significantly less FITC per cell into the afferent LN than LC

from wt (A) or p75TNFR-deficient mice (C). Mice treated with solvent alone were used as controls (shaded). For each experiment the number of FITC-positive cells and the amount of antigen uptake defined as mean fluorescence (MF), were calculated within the marker region M1. One representative experiment out of three independent experiments is shown.

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P. Seiler, G. Plenz, M.C. Deng
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cyclic AMP, prostaglandins, nitric oxide, interleukin-10, tumor necrosis factor-a, interferon-g.

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Development of allergic contact dermatitis requires activation of both tumor necrosis factor-receptors.

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allergic contact dermatitis, p75TNF receptor, p55TNF receptor, Langerhans cells, dendritic cells.

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interleukin-6, cord blood, gene polymorphism, inflammatory mediators.

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HCV-RNA, interleukin-10, H9 T cells, CD81, capsid mutation, protein kinase C.

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neuroblastoma, immunotherapy, gene therapy, cytokine, IL-1b, TNF-a.

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colorectal cancer, tumour-infiltrating lymphocytes, cytokines, gene expression, RT-PCR.

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intestinal mucosa, Crohn's disease, interleukin-18, caspase-1/ICE, immunohistochemistry, reverse transcription polymerase chain reaction.

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TNF, cytokine, LPS.

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apoptosis, caspases, Hsp27, Hsp70, T lymphocytes.

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MRC5, fibroblasts, TNF receptor, RT-PCR, binding, flow cytometry.

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cytokines, lipocalin, IL-9, 24P3.

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IL-10, recombinant, rat, cytokines.

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