Common Pathogenetic Pathways in Allergic and Irritant Contact Dermatitis

Jochen Brasch, Jan Burgard, and Wolfram Sterry
Department of Dermatology, University of Kiel, Kiel, FRG

Despite their different pathogeneses, allergic and irritant contact dermatitis show a remarkable similarity with respect to clinical appearance, histology, and immunohistology. To further analyze this apparent contradiction, our study was designed to meticulously compare cellular infiltrates in irritant and allergic patch-test reactions by immunostaining with a broad panel of monoclonal antibodies. For this purpose, skin biopsies from allergic and irritant patch-test reactions of similar inflammatory degree were obtained from the same probands.

We found that after 72 h both types of reaction were characterized by an identical dermal infiltrate consisting mainly of memory T cells, many of which were activated, and macrophages. Dermal and epidermal Langerhans cell density and HLA—DR expression of keratinocytes were also virtually identical. Our results show that antigen recognition by specific memory T cells as well as irritants can finally induce the same pattern of inflammation, including activation of T cells obviously independent of exogenous antigen.
J Invest Dermatol 98:166–170, 1992

Although induced by completely different mechanisms, allergic and irritant contact dermatitis are remarkably similar on clinical, histologic, and immunophenotypical grounds [1–5]. The correct assessment of allergic and irritant contact dermatitis may pose considerable problems in dermatologic practice, and furthermore can cause difficulties when differentiating allergic and irritant patch test reactions. From a pathogenetic point of view, however, it is difficult to explain how the antigen-specific activation of T cells will result in the same type of inflammation as the antigen- and thus T-cell–independent effects of topically applied irritants. Therefore, we decided to meticulously investigate these two types of reactions by directly comparing allergic and irritant reactions of similar clinical degree from the same individuals, using a large battery of monoclonal antibodies directed against numerous surface, intracellular, and nuclear antigens.

Specifically, we expected to find differences in the activation state or type of immigrating T cells, as well as differences in localization and frequency of accessory cells.

In this investigation, we can demonstrate that there exists no phenotypical difference between allergic and irritant patch tests from the same patients. Particularly, T cells in irritant patch-test reactions showed the same phenotype as in allergic patch tests. Moreover, no differences regarding the participating accessory cells could be demonstrated.

Manuscript received February 20, 1991; accepted for publication August 1, 1991.

Reprint requests to: J. Brasch, Universitäts-Hautklinik, Schittenhelmstrasse 7, D 2300 Kiel, FRG.

Abbreviations:
G-CSF: granulocyte colony–stimulating factor
GM-CSF: granulocyte/macrophage colony–stimulating factor
IL: interleukin
INF: interferon
LC: Langerhans cell
MoAb: monoclonal antibody
SLS: sodium lauryl sulfate
TCR: antigen-specific T-cell receptor

Based on these findings we propose that different initiating events activate common amplification mechanisms in the skin, resulting in identical, stereotypic inflammatory pathways that include T-cell participation independent of exogenous antigen.

MATERIALS AND METHODS

Probands and Test Procedure Informed consent was given by seven probands who had previously shown positive patch-test reactions to various allergens (Table I). All probands were re-challenged epicutaneously with their known allergen (test concentrations in white petrolatum [Table I]) and synchronously with aqueous solutions of sodium lauryl sulfate (SLS) 1%, 2%, and 5%. Both allergens and SLS were applied for 24 h with Finn chambers on the upper back. After 72 h, two 4-mm punch biopsies were obtained from each proband, one from the allergic patch-test reaction and one from that irritant reaction to SLS, which clinically had an intensity of inflammation equal to the latter. This means that, determined by clinical inspection, the same degree of intense erythema and moderate infiltration without vesiculation was seen in the biopsied allergic and irritant reaction of one proband, and that according to the criteria of the International Contact Dermatitis Research Group [6] all reactions were classified as moderate allergic (++) or irritant at the final reading. The biopsies were snap-frozen in liquid nitrogen and stored at −20°C until further processing.

Staining Procedure and Evaluation of Slides Immunohistochemical stainings were performed on 6-μm cryostat sections with a panel of monoclonal antibodies (MoAb) (Table II). Reactivity was visualized using a standard biotin-avidin immunoperoxidase technique from a commercially available kit (VectaStain). Additionally, double labeling with KiM8 was performed by alkaline-phosphatase conjugation (Dakopatts). Percentages of the various dermal infiltrate subpopulations were determined by analyzing at least 200 cells per section; epidermal cell densities were counted per 0.1 mm^2. Cells clearly representing endothelial cells or fibroblasts were not evaluated.

Monoclonal Antibodies Monoclonal antibodies, their specificity as well as their source, are given in Table II.

Table I. Probands and Test Substances

Proband Number	Age (years)	Sex	Allergen	Concentration of SLS[a]
1	60	M	Balsam of Peru 25%	2%
2	76	F	Balsam of Peru 25%	5%
3	74	M	Wool alcohols 100%	2%
4	42	F	Balsam of Peru 25%	5%
5	68	M	Nickel sulphate 5%	5%
6	50	F	Propyleneglycol 5%	5%
7	37	F	Bepanthen cream 100%[b]	1%

[a] Concentration of sodium lauryl sulfate used for biopsied irritant reaction.
[b] Bepanthen-Roche-cream is a commercially available preparation for treatment of superficial wounds, containing dexpanthenol.

RESULTS

The different cell types participating in positive allergic patch-test reactions have been investigated and published previously by several groups including our own [2,3,7–9]. Our present study concerning this type of reaction, which is therefore briefly summarized, confirms these earlier findings.

In allergic patch tests, CD1a+ Langerhans cells (LC) in the dermis contributed approximately 20% of the infiltrate (Fig 1). The majority of the dermal cells was made up of helper T cells of the memory phenotype and by cells of the monocyte macrophage series in the same general location as T cells, but CD8+ cells were also seen (Figs 1 and 2). T cells expressing gamma/delta receptors were below 5%. A major fraction of the infiltrating dermal cells was activated and expressed the transferrin receptor (CD71) (Figs 3 and 4) and interleukin 2 (IL-2) receptor α chain (CD25) (Fig 3); some of them even expressed the proliferation-associated nuclear antigen Ki-67 (Fig 3). Double staining for activation markers and KiM8 revealed that activated cells were mainly lymphocytes (Fig 4).

Epidermal LC density in allergic patch tests was reduced to 10.6 cells/0.1 mm^2, s = 5.8). Nearly all epidermal T cells (density for Leu4+ cells, 6.8/0.1 mm^2, s = 4.1) were of the helper and memory type (Leu3a+, UCHL1+), whereas naive or suppressor T cells did not relevantly contribute.

In the irritant patch-test reactions from the same patients (Figs 1–3), unexpectedly virtually identical findings were observed.

Most of the dermal round cells were positive for CD2 (approximately 70%), CD3 (approximately 80%), CD5 (approximately 75%), and CD4 (approximately 75%) (Fig 2). A minority (approximately 18%) was positive for CD8. CD45RA could be used as a marker for naive T cells, because B cells, which also express CD45RA, were represented only very scarcely (Fig 2). Naive T cells were below 5%, whereas the majority of the infiltrate expressed the CD45RO antigen, thus characterizing them as T cells of the memory phenotype (Fig 2). Gamma/delta receptor expression was only very scarcely detected.

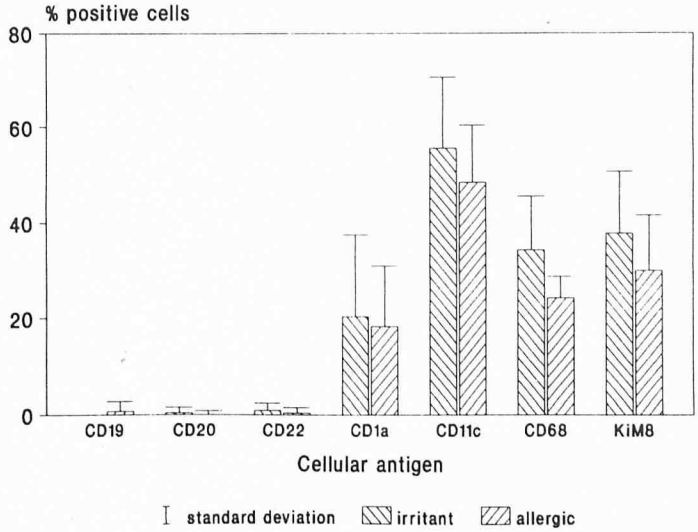

Figure 1. B cells, Langerhans cells, and macrophages in the inflammatory dermal infiltrates of irritant and allergic patch-test reactions. Discriminating cellular antigens were stained with the appropriate monoclonal antibodies (for specification see Table II). Columns represent arithmetic means of percent positively stained cells with standard deviation (n = 7).

Langerhans cells (CD1a+) represented a substantial component of the dermal infiltrate, ranging from 10 to 30% (Fig 1). Macrophages were regularly present, making up approximately 50% (CD11c) or 30% (CD68, KiM8) of the infiltrate (Fig 1).

Remarkably, dermal cells in irritant patch-test reactions also showed signs of activation to the same degree as in allergic patch-test reactions (Fig 3). Most of the infiltrating cells were HLA-DR+,

Table II. List of Monoclonal Antibodies (MoAb) Used

CD Designation	MoAb	Specificity	Source
1a	Leu6	Thymocytes; resting Langerhans cells	BD[a]
2	Leu5b	T cells	BD
3	Leu4	T cells	BD
5	Leu1	T cells	BD
4	Leu3a	Helper T cells; activated macrophages and Langerhans cells	BD
8	Leu2a	Suppressor T cells	BD
11c	LeuM5	Macrophages; activated CD8+ T cells	BD
19	Leu12	B cells	BD
20	Leu16	B cells	BD
22	D.CD22	B cells	Dakopatts
25	α-tac	α-chain of interleukin 2 receptor	BD
CD45R0	UCHL1	Memory T cells; activated macrophages	Dakopatts
CD45RA	Leu18	Naive T cells; B cells	BD
CD54	anti-ICAM	Intercellular adhesion molecule-1	Immunotech
68	KiM6	Macrophages	M.R. Parwaresch, Kiel
71	OKT9	Transferrin-receptor	Ortho
	KiM8	Macrophages	
	KLA-DR	Monomorphic determinant of HLA-DR heterodimer	BD
	Leu10	Monomorphic determinant of HLA-DQ heterodimer	BD
	TCRδ1	δ-chain of gamma/δ T cell antigen receptor	T Cell Sciences
	Ki-67	Proliferation associated nuclear antigen	Dakopatts

[a] BD, Becton Dickinson.

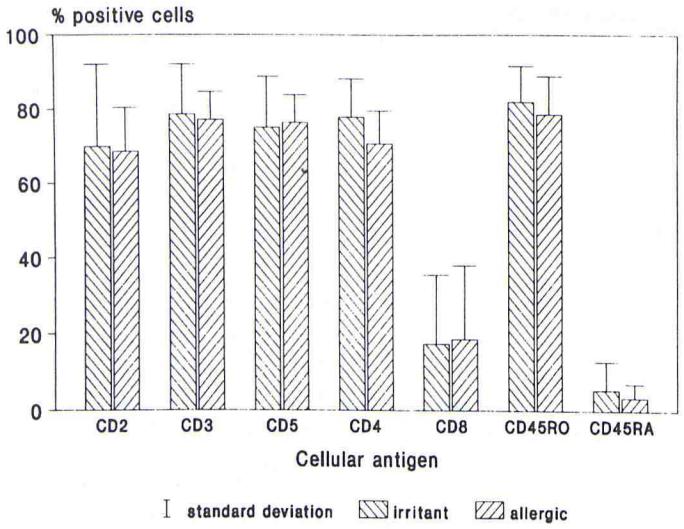

Figure 2. Different T-cell types in the inflammatory dermal infiltrates of irritant and allergic patch-test reactions. Discriminating cellular antigens were stained with the appropriate monoclonal antibodies (for specification see Table II). Columns represent arithmetic means of percent positively stained cells with standard deviation (n = 7).

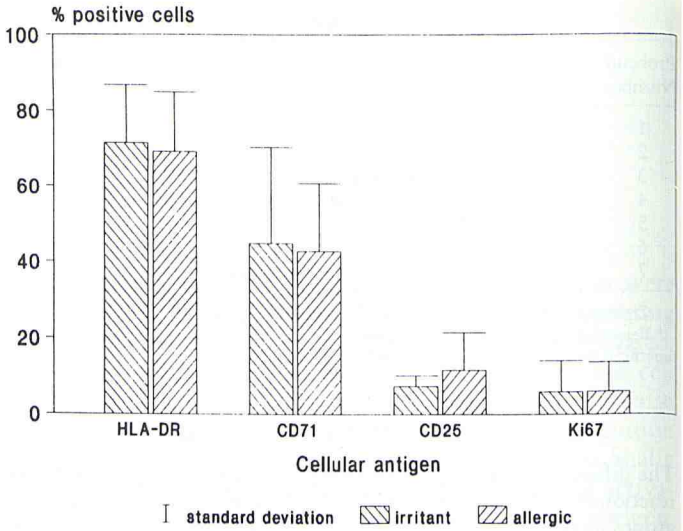

Figure 3. Activated cells in the inflammatory dermal infiltrates of irritant and allergic patch-test reactions. Cellular antigens representing activation markers were stained with the appropriate monoclonal antibodies (for specification see Table II). Columns represent arithmetic means of percent positively stained cells with standard deviation (n = 7).

and a considerable amount (approximately 45%) were bearing transferrin receptors (CD71) and interleukin-2 receptor α chains (CD25, approximately 9%, Fig 5). Most of these activated cells were lymphocytes, being negative for KiM8 in double staining (Fig 5). Five percent of cells were proliferating, according to the expression of the Ki-67 antigen (Fig 3).

In the epidermis of irritant patch tests LC density (11.3/0.1 mm^2, s = 5.2) and T-cell density (5.7 Leu4+ cells/0.1 mm^2, s = 4) both were equal to allergic reactions. Epidermal T cells in irritant reactions were nearly exclusively of helper and memory type, too. HLA-DR expression of cells invading the epidermis was equal in irritant and allergic reactions. In both types the vast majority of keratinocytes was negative for HLA-DR staining. ICAM-1 expression was detected focally on keratinocytes in allergic and in irritant reactions.

Differences in dermal cell densities in allergic and irritant reactions proved to be not significant when mean values calculated from all probands were compared. Furthermore, in none of the probands was there a difference in relevance between the cell infiltrates in both types of reaction.

DISCUSSION

Our results clearly demonstrate that even extensive immunostaining of all relevant cell types does not allow discrimination between irritant and allergic patch-test reactions at the time of their final reading. There is no significant difference in the percentages of subtypes of T cells, LC, and macrophages or in the activation antigens expressed by these cells.

Previous studies on this issue had revealed some conflicting data. Epidermal CD1a+ Langerhans cells have been reported to decrease

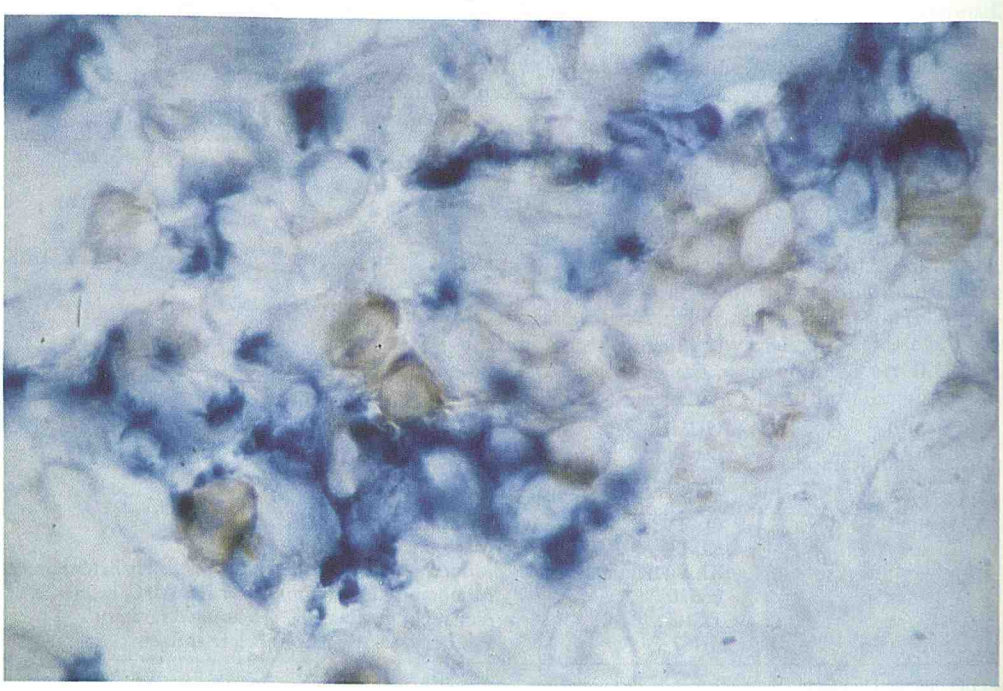

Figure 4. Double labeling of transferrin receptors (OKT9, immunoperoxidase, *brown color*) and macrophages (KiM8; alkaline phosphatase, *blue color*) in an allergic patch-test reaction. Transferrin receptors are expressed mainly by lymphocytes and not by macrophages.

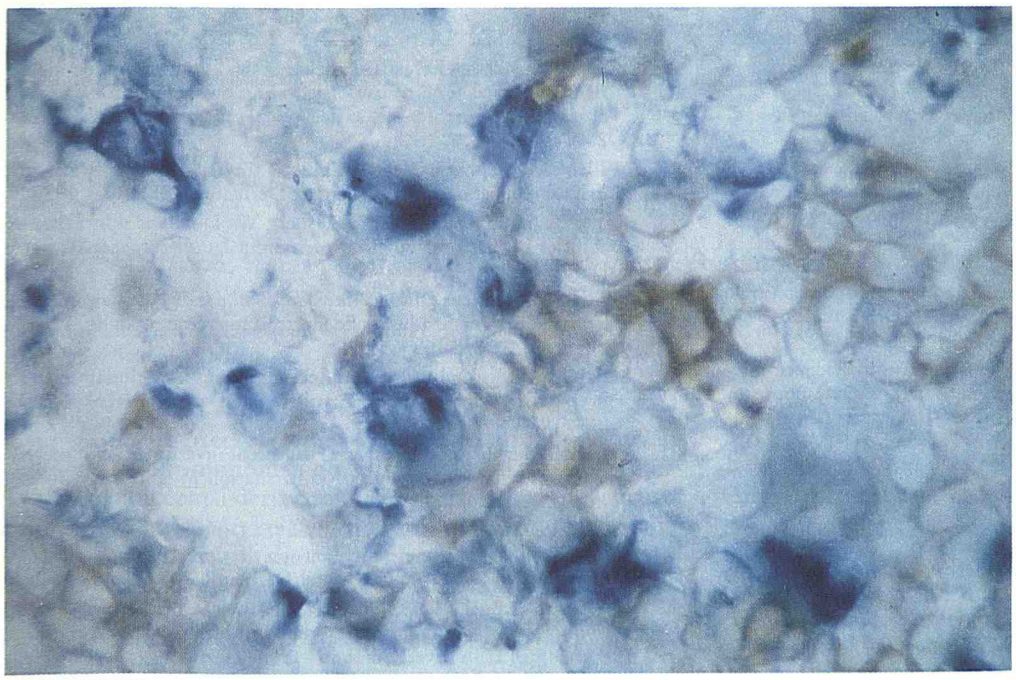

Figure 5. Double labeling of IL2-receptors (alpha-tac, immunoperoxidase, *brown color*) and macrophages (KiM8; alkaline phosphatase, *blue color*) in an irritant patch test (same proband as Fig 4). IL2-receptors are expressed mainly by lymphocytes and not by macrophages.

in allergic [10,11] and irritant [12,13] reactions but also to increase in both types [14,15]. Our data now show a reduction of epidermal LC density in both types of reaction to approximately 20% of normal skin values as determined by us previously [9]. Furthermore, HLA-DR expression on keratinocytes was observed in 9 of 14 allergic reactions, but not in irritant ones [7]. Other groups, however, were not able to find significant differences between allergic and irritant reactions [2,3]. This is now substantiated by our extensive immunophenotypic studies comprising both types of reactions in the same individuals. There is, however, general agreement on the fact that in allergic contact dermatitis [2,3,11], as in other inflammatory dermatoses [16,17], mainly memory T cells are involved.

In the sensitization phase of allergic contact dermatitis LC are supposed to take up the hapten, migrate to draining lymph nodes, and trigger a T-cell response by presenting processed antigen to naive T cells, thereby inducing their maturation into memory T cells [16,18]. These memory T cells then migrate to antigen-exposed sites of the skin; in contrast, naive T cells, which make up 50% of peripheral blood T cells, are not able to enter the skin in relevant numbers [8]. The primary immigration into the skin is antigen independent, because negative patch-test reactions also contain small numbers of memory T cells and monocytes [9]; in the case of antigen recognition, amplification occurs and leads to the immigration and activation of large numbers of monocytes and T cells, which were shown to produce gamma-INF and IL-2 [19]. In addition, a significant IL-1 release was measured at sites of human cutaneous allergic reactions [20]. Most interestingly, most of these T cells are not antigen specific. For example, in allergic patch tests, antigen-specific memory T cells made up only 7–15% of T cells [21] or even less than 1% [22,23]. Nevertheless, a considerable number of the infiltrating T cells are activated (Figs 3 and 4).

Skin damage by SLS as a standard substance for elicitating irritant reactions has been well investigated [24–30]. Concentrations up to 5% SLS increase epidermal mitosis [25] and change keratinocyte morphology, suggesting disturbances of their metabolism and differentiation [24,29]. For skin irritation variation among different SLS qualities and differences in individual susceptibility towards SLS [27,28], adaptation of the SLS patch-test concentration to the individual clinical response as performed in this study is essential when results from different probands are to be compared.

Although certainly not all irritants initially act via a common mechanism [31], a diversity of unrelated chemicals, when applied in suitable concentrations, finally results in moderate skin reactions that share some characteristics: a mild damage to keratinocytes, a predominantly mononuclear dermal infiltrate, and apposition of lymphocytes with LC [29,32]. Perhaps such a moderate irritation of epidermal cells could stimulate them to release similar mediators of inflammation. IL-1 is stored in normal stratum corneum [33], from which it might be released by cell-damaging irritants [34]. IL-1 and IL-8 activity were elevated in epidermal homogenate during both allergic and irritant skin reactions [35,36]; IL-8 has been shown to exert T-cell chemoattractive effects [37]. Additional mediators that are known to be produced by keratinocytes such as IL-3, IL-6, G-CSF, M-CSF, GM-CSF, and TNFα [34,38,39] may also participate [40,41]. The pathways involved in antigen-independent T-cell activation include the surface molecules CD2 [42,43], CD28 [44,45], and UM4B4 [46]; their exact role in the setting of contact dermatitis remains to be analyzed. The minimal expression of gamma/delta receptors by the T cells involved argues against their activation by heat-shock proteins [47].

The described similarity of cellular infiltrates in irritant and allergic contact dermatitis suggests that once an initiating level of activation either via T cells or epidermal cells has been reached, common subsequent pathogenetic pathways include continuous T-cell accumulation and activation independent of exogenous antigen.

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