Immunological and Molecular Mechanisms of Photoallergic Contact Dermatitis

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Abstract: Photocontact dermatitis is one of the major occupational skin diseases and an undesirable adverse effect produced by chemicals and drugs in our environment. This dermatitis is caused by skin application of photosensitive agents plus ultraviolet light irradiation. There exist both primary irritant and allergic mechanisms in this dermatosis. While the former is induced by the phototoxic reactions, the latter allergic type is mediated by Langerhans cells, T cells, various cytokines and chemokines, and thus occurs via a well-orchestrated and well-elucidated immunological mechanism. The photoallergic type has a higher incidence and more severe skin eruptions than the primary irritation. Photoconjugation of epidermal cells with a photohaptenic halogenated chemical is the initial step, and Langerhans cells serve as antigen-presenting cells. Causative photohaptens are bound to MHC class II molecules/self peptide on Langerhans cells upon exposure to UVA. The photomodified Langerhans cells sensitize and elicit antigen-specific T cells that mediate photoallergy. Thus, this photoallergy is induced by well-orchestrated photochemical and immunological mechanisms.

Key words: photoallergy, contact dermatitis, UVA, contact hypersensitivity, Langerhans cell.

(Received 28 July 2003, accepted 25 September 2003)

Introduction

Many skin diseases are caused by occupation- or environment-related chemical compounds or conditions. These include: 1) contact or photocontact dermatitis, mediated by primary irritant or allergic mechanism against chemicals; 2) acneiform eruption, evoked by oil, halogenated chemicals or tar; 3) dyscoloration, induced by arsenic, tar, alkylphenol or others; 4) chronic radiation dermatitis, manifesting with a poikilodermatous eruption; 5) cutaneous neoplasms, yielded by arsenic, tar, radiation or other mutagenic modalities; and 6) skin infection, caused by various types of microorganisms [1]. Among these occupational skin disorders, contact dermatitis is the major skin disorder, and photocontact dermatitis is a specialized form of this skin disease [2]. Photocontact dermatitis is divided into two subtypes: phototoxic and photoallergic contact dermatitis, with the latter being clinically more common than the former. It is sometimes difficult to diagnose this photosensitivity, although its incidence is
relatively high. Great attention must be paid to photoallergic contact dermatitis, as some investigators have stated that photoallergy, chloracne, occupational leukoderma and neoplasia are special occupational problems [3].

In general, photoallergy to exogenous agents is an immunological consequence induced by the administration of photoallergic substances and exposure to ultraviolet (UV) light. Two major diseases are evoked by photoallergic mechanisms, photoallergic contact dermatitis and drug photoallergy [4]. The former is induced by skin application of photosensitive contactants and follow UVA irradiation, while the latter disease is caused by oral photosensitive drugs plus UVA. This review aims to highlight photoallergic contact dermatitis focusing on its immunological and molecular mechanisms in the interaction between photoantigen-presenting cells and T cells.

**Causative agents and Clinical manifestations**

Various chemicals have been reported to evoke photoallergic contact dermatitis, as shown in Table 1. Historically, the use of halogenated salicylanilide and related compounds employed as topical antimicrobial agents resulted in a large number of patients with photoallergic contact dermatitis [5—7]. The elimination of these germicides from the market reduced considerably the number of such patients. Recent causative agents of allergic photocontact dermatitis are topical non-steroidal anti-inflammatory drugs, such as ketoprofen [8] and suprofen [9], and cosmetic or sunscreen products such as benzophenone [4].

Patients develop an eczematous eruption exhibiting erythema and papules/vesicles, and occasionally bullae, at the skin sites where a photocontactant is applied and solar light is irradiated. The action spectrum of this photosensitivity is mainly UVA light. When the patients are photosensitized with a certain chemical, they exhibit positive photopatch test by the application of that chemical and exposure to UVA. Histologically, the skin lesion is an eczematous tissue reaction characterized by the infiltration of epidermal spongiosis, exocytosis and a dense mononuclear cell into the dermis [10].

**Photoantigen formation**

Since photoallergic contact dermatitis is an immunological disorder, it is necessary for causative chemicals to become antigens or photoantigen upon exposure to UVA. As illustrated in Fig. 1, two theories have been put forward to explain the formation of photoantigen [4]. One is that the photosensitizer is a photohapten, which binds covalently to the carrier protein via the formation of free radicals resulting from UV irradiation. Thus, photohaptens are virtually the same as ordinary haptens, except for the requirement of UV irradiation for covalent coupling with protein. Another theory suggests that the photosensitizer is a prohapten, which is converted to a complete hapten by UV irradiation, and the UVA-modified
Table 1. Causative agents of photoallergic contact dermatitis

**Antimicrobial agents (mainly halogenated salicylanilides)**
- Tetrachlorosalicylanilide (TCSA)
- Dibromosalicylanilide (DBS, Dibromosalan)
- Tribromosalicylanilide (TBS)
- Bithionol (Thiobisdichlorophenol)
- Trichlorocarbanilide (TCC, Trichlocarban)
- Tribromosalicylanilide (TBS)
- Bithionol (Thiobisdichlorophenol)
- Trichlorocarbanilide (TCC, Trichlocarban)
- Tribromosalicylanilide (TBS)
- Bithionol (Thiobisdichlorophenol)
- Hexachlorophene
- Chloro-2-phenylenol (Dowicide 32)
- Fenticlor (Thiobischlorophenol)
- Multifingin (Bromochlorosalicylanilide, BCSA)
- Jadit (Buclosamide, Butylchlorosalicylamide)
- Triclosan
- Chlorhexidine
- Dichlorophene
- Sulfanilamide

**Perfumes**
- Musk ambrette
- 6-Methylcoumarin
- Sandalwood oil

**Sunscreens**
- Para-amino-benzoic acid (PABA)
- Octyl-dimethyl PABA (Padimate O)
- Amyl-dimethyl PABA (Padimate A)
- Glycerol PABA
- Benzophenone (especially Benzophenone-3 = Oxybenzone)
- Butyl-methoxydibenzoylmethanes (Parsol 1789)
- Digalloyl trioleate
- Cinnamates (Cinoxate)

**Non-steroidal anti-inflammatory drugs**
- Ketoprofen
- Suprofen

**Hair dye**
- Para-phenylenediamine (PPD)

A substance can bind to protein. Therefore, in the case of photohaptens, UVA-preirradiated chemicals are incapable of binding to protein, and a non-covalent bond between photohaptens and protein is required upon irradiation of them with UVA. Our studies have suggested that the vast majority of clinically photoallergic chemicals are photohaptens rather than prohapten-s [11–13].
Mouse model of photoallergic contact dermatitis

Mouse models of photoallergic contact dermatitis were established by several groups in the early 1980's [14, 15], and enabled researchers to elucidate mechanisms of the sensitivity because of its technical convenience and availability of accumulated immunologic information on this species. In these models, 3, 3', 4', 5-tetrachlorosalicylanilide(TCSA), a representative halogenated salicylanilide, has been used typically as photoallergen. Mice are sensitized by two daily abdominal paintings with 1% of TCSA plus UVA irradiation and challenged 5 days later on the earlobes with TCSA plus UVA. Ear swelling responses are measured 24 h after the challenge. In addition to TCSA, the photoallergic potential of other halogenated salicylanilides, such as tribromosalicylanilide and bithionol, is also detected by this mode of sensitization [16].

Murine photoallergic contact dermatitis to TCSA is genetically controlled and determined mainly by the major histocompatibility complex (MHC) [17, 18]. The H-2d haplotype is closely associated with low responders, while mice with H-2b haplotypes are high responders [18]. Such a clear-cut association of the H-2 haplotype with the degree of response has not been found in ordinary contact dermatitis to haptens. We have recently found that in photoallergic contact dermatitis to ketoprofen, a non-steroidal anti-inflammatory drug, mice with
H-2<sup>k</sup> are high responders, whereas those with H-2<sup>bd</sup> are low responders. Therefore, high responder H-2 haplotypes are different among photosensitivities to each photohaptenic chemical.

**Immunological mechanism of the photosensitivity**

Because of the ability of photohaptens to photobind to protein, cells are easily photomodified with a photohapten under exposure to UV. UVA is the action spectrum of this photo-derivatization, as protein and cells are photocoupled with photohaptenic substances by irradiation with UVA but not UVB. The main sequential events in photoallergic contact dermatitis are virtually the same as those of ordinary contact dermatitis except for the requirement of UV irradiation in sensitization and challenge (Fig. 2). Photoconjugation of epidermal cells with TCSA is the initial step in allergic contact dermatitis to TCSA. Langerhans cells (LC), which are professional antigen-presenting cells in the epidermis, play an important role and T cells sensitized by photohapten-bearing LC induce this photosensitivity [2]. Migration of TCSA-bearing LC to draining lymph nodes in the sensitization phase [19] and involvement of mast cells in the challenge phase [20] are required, as in ordinary contact dermatitis.

Murine photoallergic contact dermatitis to TCSA involves both positive and negative immunologic pathways that are restricted by I-A and I-E molecules on antigen-presenting cells.
[18, 21]. The suppressive pathway is mediated by IL-10-producing Th2 cells[21], which had been known as suppressor T cells and may correspond to recently called regulatory T cells. Sensitization with TCSA plus UVA is prone to induce Th2 cells compared to ordinary haptens[22], suggesting that the suppressive immunologic pathway is clearly detectable in this sensitivity. Antigen-specific, afferent limb-acting Th2 cells are responsible for the low responsiveness of H-2k mice. The low responsiveness of photoallergic contact dermatitis in the H-2k strain is due to the preferential activation of Th2 cells via I-Ek molecules [18].

Molecular mechanism of photoantigen presentation

In photoallergic contact dermatitis and drug photoallergy, causative photohaptens are bound to MHC class II molecules/self peptide on LC upon exposure to UVA [23]. The photomodified LC sensitize and elicit antigen-specific T cells that mediate photoallergy [24]. For example, in our murine model of fluoroquinolone photoallergy, quinolone diffuses to the epidermis. Upon UVA exposure, LC are photomodified with a given quinolone in their MHC class II-associated peptides, thereby sensitizing and eliciting TCR Vβ13-bearing T cells [25], which in turn leads to photoallergic skin reactions.

The piperazinyl(or methylpiperazinyl) group, the major side chain of quinolone linked at C7, is altered by UVA irradiation. It is thus possible that protein may be covalently bound to the piperazinyl ring during its photodegradation to form an allergic quinolone-protein complex [25]. An affinity chromatographic study using a quinolone photoaduct-specific monoclonal antibody as ligand demonstrated preferential photocoupling of FQ with a lysine-containing peptide [24]. Primed CD4+ T cells proliferated in vitro in response to LC loaded with class II (I-Aβ)-binding, lysine-containing peptides when photomodified with FQ [24]. Epicutaneous application of the FQ-phoconjugated peptide via barrier-disrupted skin was able to sensitize mice for subsequent elicitation of photoallergy evoked with systemic FQ and UVA. This study suggested that lysine affords FQ photocoupling of peptides, and FQ-photomodified peptides on class II molecules stimulate pathogenetic T cells in FQ photoallergy.

The topical application of TCSA and irradiation with UVA not only produce the formation of photoantigen but also promote the antigen-presenting ability of LC (Fig. 3). The combination of TCSA painting and UVA exposure to the skin of mice elevates the expressions of MHC class II and CD86 markedly and those of CD80 and CD54 slightly on the surface of LC [26]. There exist subpopulations of LC that express MHC class II and CD86 at high levels. Since neither TCSA painting nor UVA exposure alone enhances the expression, both treatments are essential for enhancement. MHC class II and CD86 molecules are mandatory for the antigen-presenting function of LC. Therefore, as ordinary haptens[27], photohaptens are capable of inducing immunocompetent molecules on antigen-presenting cells when irradiated with UVA.
Fig. 3. Formation of photoantigen and promotion of antigen-presenting ability in Langerhans cells treated with photohapten and UVA.

Photoallergy to exogenous agents is not only important in occupational and environmental medicine but also useful to explore the mechanisms underlying immunity to chemicals. Further investigation of this sensitivity may give us intriguing information on occupational chemical use.

References


Photoallergic Contact Dermatitis

光アレルギー性接触皮膚炎の免疫学的分子機構

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要　旨：外的化学物質が皮膚に塗布され、紫外線(UV)特にUVAが同皮膚に照射されて生じる皮膚炎を光接触皮膚炎と言う。光接触皮膚炎には光毒性機序によるものと光アレルギー性機序によるものとがあり、後者の方が臨床的に高頻度である。通常の接触皮膚炎と同様に光接触皮膚炎においてもランゲルハーンス細胞(LC)は抗原提示細胞として働き、ほとんどの光接触皮膚炎を起こす化学物質は光ハプテンとしての性格を持つ。これはUVA照射下において蛋白と共有結合し、LCのMHCクラスII分子に提示される。光抗原の形成とその提示機構は、光接触皮膚炎において独特のものである。光ハプテンが光結合した自己ベプチドはT細胞に対する抗原と成り得る。さらに光ハプテンとUVAはLCのクラスII,B7分子の発現を高め抗原提示能を亢進させる。

キーワード：光アレルギー、接触皮膚炎、紫外線、接触過敏症、ランゲルハーンス細胞。