

CONTEMPORARY REVIEW

Chemical or Drug Hypersensitivity: Is the Immune System Clearing the Danger?

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ABSTRACT

Hypersensitivity reaction or allergy, initially perceived as a secondary disorder, is now believed to be a major public health concern. For instance, contact dermatitis is a type IV delayed-type hypersensitivity reaction to skin allergens. An estimated 15%–20% of the general population has acquired contact allergy. To maintain immune tolerance, our immune system needs to differentiate between harmful non-self and innocuous non-self. Living organisms have developed during their evolution a set of biological mechanisms to protect them from the “outside”: physical barrier, inflammation, cell-based mechanisms, metabolism and elimination, and biochemical pathways such as glutathione. The innate and adaptive immune systems are also involved in the protection from the “outside” by mounting specific or non-specific responses leading to the clearance of dangerous triggers such as viruses, bacteria, or parasites. In the case of chemical or drug allergy, is our immune system clearing the danger resulting from environmental exposure to these harmful chemicals with a true immune response? Is the immune system then triggered specifically for its role: clearing a specific problem? Alternatively, should we perceive chemical or drug hypersensitivity as an accident with uncontrolled consequences leading to immunopathology?

Key words: chemical allergy; immunotoxicology; immunotoxicity; immunotoxicology; immunopathology; hypersensitivity.

Hypersensitivity reactions can be classified into 2 categories depending on if they are mediated by the immune system or not. When mediated by the immune system, hypersensitivity reactions are termed allergy. Allergy is a major public health concern, pushing specialists to suggest a worldwide epidemic problem (Tanno *et al.*, 2016a). When provoked by exposure to chemicals or drugs, “Allergy” is defined as a clinical manifestation due to an “inappropriate” immune response provoked by the exposure to low-molecular weight chemicals (<1000 Da). Clinical manifestations are very diverse with systemic reactions such as the anaphylactic shock and involve a diversity of target organs. These target organs are mainly the respiratory track (rhinitis, asthma), the liver (immune-mediated hepatitis) and the skin (allergic contact dermatitis [ACD]; Stevens-Johnson syndrome [SJS]; toxic epidermal necrolysis [TEN]; drug reaction with eosinophilia and systemic symptoms [DRESS]) (Peiser *et al.*, 2012; Tanno *et al.*, 2016b). Allergic reactions can be potentially life-threatening, such as anaphylactic shock, DRESS, SJS, and

TEN (White *et al.*, 2015). ACD is an allergic reaction to chemical sensitizers that encounter the skin. An estimated 15%–20% of the general population has acquired contact allergy (Kaplan *et al.*, 2012). It is also a major cause of occupational skin disease affecting the life of exposed individuals with an estimated newly reported annual incident of 0.5–1.9‰ in Europe (Kaplan *et al.*, 2012; Peiser *et al.*, 2012). The highest incidence is found in hairdressers, metal workers, healthcare workers, food industry workers, construction workers, cleaners, and painters (Diepgen, 2012). Common contact allergens may be inorganic chemicals, such as nickel, and organic chemicals, such as those found in fragrances and dyes (*p*-phenylenediamine [PPD] or methylisothiazolinone) (Kaplan *et al.*, 2012).

The original Gell and Coomb's classification divided hypersensitivity allergic reactions into four subtypes according to the type of immune response and the effector mechanism responsible for cell and tissue injury (Uzzaman and Cho, 2012). Type I reactions are mediated by IgE antibodies and mediators released

from mast cells and basophils and the onset of the clinical outcome is rapid (immediate hypersensitivity). Type IV reactions are delayed T-cell-mediated reactions. Nevertheless, whatever is the type of clinical manifestations there are always 2 phases necessary for an allergic reaction to occur. The first phase is the sensitization phase characterized by the appearance of a specific immune reaction directed to the chemical in most cases involving specific T lymphocytes and antibodies but without clinical manifestation; it is common and dose dependent. The second phase is the elicitation phase characterized by the clinical manifestation and occurring in a small percentage of patients (Kaplan *et al.*, 2012).

Living organisms have developed during their evolution a set of biological mechanisms to protect them from the “outside”: physical barrier, inflammation, cell-based mechanisms, metabolism and elimination, and biochemical pathways such as glutathione. The innate and adaptive immune systems are also involved in the protection from the “outside” by mounting specific or non-specific responses leading to the clearance of dangerous triggers such as viruses, bacteria, or parasites. To this attempt, it is now well established that our immune system must be able to distinguish self from non-self and to differentiate harmful non-self from innocuous non-self. Maintaining an immune tolerance in the latter case is mandatory to avoid uncontrolled consequences leading to immunopathology (Aliberti, 2016; Matzinger, 2012, 1994).

However, in the case of chemical or drug hypersensitivity, is our immune system clearing the danger linked to the exposure to harmful chemical entities? Should we perceive chemical or drug hypersensitivity as an accident with uncontrolled consequences leading to immunopathology or as a true immune response with the immune system being triggered specifically for its role: clearing a problem?

THE DANGER MODEL: HOW THE IMMUNE SYSTEM CAN DISTINGUISH BETWEEN HARMFUL AND NON-HARMFUL ANTIGENS?

The immune system being triggered by continuous exposure to antigens from outside it is important to recognize what is dangerous and needs to be eliminated from what can be tolerated in the body, ie, food and environmental antigens. In 1994, the immunologist Polly Matzinger came up with a controversial idea: “Alarm signals released from injured and dying cells can kick our immune system into high gear even when no microbial threat is evident” (Matzinger, 1994). These “Alarm signals” are now termed “danger signals.” They are necessary for the dendritic cells (DC), the pivotal antigen-presenting cell (APC), to recognize a “harmful” cellular environment created by the antigen or in which the antigen is present, thus informing that an effector immune response needs to be mounted for clearing the “danger.” One major consequence of the recognition of the danger signals by DC is the acquisition of an “effector” phenotype versus a “tolerogenic” one. The latter will be adopted by DC when the antigen is present in the absence of danger signals (Matzinger, 1994, 2012). These danger signals can be exogenous (pathogen-associated molecular patterns, eg, lipopolysaccharide [LPS]) or endogenous (damage-associated molecular patterns [DAMP]), constitutive or inducible, intracellular (heat shock proteins [HSP]), or secreted (low-molecular weight hyaluronic acid [MWH] and high-mobility group box 1 [HMGB-1]) from distressed and injured cells (Tsan and Gao, 2004). Other danger signals include the inflammasome and proinflammatory cytokines (tumor necrosis factor [TNF]- α , interleukin [IL]-1) (Franchi *et al.*, 2012; Man and Kanneganti, 2015; Ryan *et al.*, 2007).

Multiple “innate immune receptors” exist inside and outside the DC or other innate immune cells. They constitute the pattern recognition receptor (PRR) such as Toll-like receptor (TLR), NOD-like receptors (NLR), C-type lectin receptors, and RIG-I-like receptors (Iwasaki and Medzhitov, 2015; Kawai and Akira, 2010; Leifer and Medvedev, 2016; Walsh and Mills, 2013). Indeed, each PRR can bind to many different kinds of molecules deriving from the outside environment (bacteria, virus, fungus, etc.) or from dying cells (Iwasaki and Medzhitov, 2015; Kawai and Akira, 2010; Martin, 2014, 2015). For instance, TLR4 is a receptor for LPS, HSP70, and low MWH (Matzinger and Kamala, 2011).

HOW CHEMICALS ARE CREATING A «DANGER» RECOGNIZED BY DCs LEADING TO AN ADAPTIVE IMMUNE RESPONSE?

Hypothesis 1: Can chemical allergens directly activate dendritic cells and play the role of danger signals?

In addition to their ability to present the processed antigen to T cells, DCs should express costimulatory molecules and release soluble factors that drive T cells from a naive to an effector phenotype, thus promoting sensitization to the chemical (Kaplan *et al.*, 2012; Walsh and Mills, 2013)

A. Modifications of DC phenotype. Chemical allergens can directly modify DC phenotype leading to different extracellular receptor changes, including co-stimulatory molecules (CD86, CD80, and CD40), chemokine receptors (CCR7) and adhesion molecules (CD54). Major histocompatibility complex (MHC) class II molecules (Human leukocyte antigen-antigen D related, HLA-DR) expression is also augmented in addition to cytokine production (IL-12, IL-6, and TNF- α). These modifications allow DC migration from peripheral tissues to regional lymph nodes and clonal expansion of specific T cells. For instance, using human CD34⁺-derived DC, nickel and dinitrochlorobenzene (DNCB) induced CCR7 expression and DC migration in response to CCL19 (Boislève *et al.*, 2004). DNCB, trinitrochlorobenzene (TNCB), nickel, cobalt, eugenol (eu), and cinnamaldehyde (cin) induced CD54 expression in human monocyte-derived DC (mo-DC) (Coutant *et al.*, 1999; de Bourayne *et al.*, 2017; Manome *et al.*, 1999; Tuschl *et al.*, 2000). Furthermore, all these chemical sensitizers upregulated the expression of at least one costimulatory molecule, CD83 protein, and HLA-DR in different in vitro human DCs models (Antonios *et al.*, 2009; Boislève *et al.*, 2005; Coutant *et al.*, 1999; Manome *et al.*, 1999; Tuschl *et al.*, 2000). DNCB and nickel were also able to induce IL-6, IL-1, IL-8, TNF- α , and IL-12p40 production in human DCs (Ade *et al.*, 2007; Aiba *et al.*, 1997; Antonios *et al.*, 2009, 2010; de Bourayne *et al.*, 2017; De Smedt *et al.*, 2001; Manome *et al.*, 1999; Rachmawati *et al.*, 2013). The case of drugs is more complex because most drugs are not chemically reactive. Sulfamethoxazole (SMX) and its protein-reactive metabolite nitroso-SMX increased CD40 expression, but not CD80, CD83, or CD86, on the surface of human DCs (Sanderson *et al.*, 2007). Interestingly, DCs-metabolism inhibition prevented the increase in CD40 expression with SMX, but not with nitroso-SMX demonstrating a link with the intracellular metabolism. In vitro, a danger environment significantly increased the formation of SMX-protein adducts in APC, illustrating that danger signals can enhance the formation of intracellular SMX-protein adducts in human APC (Laverne *et al.*, 2009). Same results have been found for beta-lactams (Sebastian *et al.*, 2012). Nevirapine (NVP) treatment, a non-nucleoside reversed transcriptase inhibitor indicated for the

Allergic and hypersensitivity reactions to chemicals and drugs

1- A true immune response with the immune system being triggered for its role: clearing a problem?

- Reactive chemicals and metals are dangerous entities
–Important to avoid prolonged contact that could lead to serious health problems
- Very diverse entities are able to induce chemical allergy
–There are some evidences that chemicals have found very specific ways to activate the immune system: direct TLR activation, modification of the cellular microenvironment (low MSHA, ATP, HMGB-1, cytokines, etc.)
- Hapten-protein complexes are processed and specifically associated to HLA molecules
–Specific T-cell antigen receptors for chemicals exist

2- An accident with uncontrolled consequences leading to immunopathology?

- Role for inflammation = nonspecific inflammation gives a sufficient trigger to provide necessary “danger signals” for the DC playing a role in response to a bystander antigen (chemical, drugs)
- Chemicals are reactive = bind to peptides present in the HLA pocket creating new antigens (self-modified) without any specificity
- Drugs possess off-target activity on HLA and TCR: pharmacological reactions can lead to severe hypersensitivity reactions

treatment of HIV, is associated not only with idiosyncratic liver toxicity but also with mild-to-severe skin rashes. Interestingly, NVP metabolites can covalently bind in the liver but the 12-OH-NVP sulfate formed in the skin provoked NVP-induced skin rashes (Sharma *et al.*, 2013). Recent work showed that 12-OH-NVP is a necessary reactive intermediate and also provided danger signals (Zhang *et al.*, 2013).

B. Activation of specific cell signaling pathways in DC. How chemical sensitizers can directly modulate human DC phenotype? It is well established that DC phenotype is tightly regulated by signaling pathways as exemplified with danger signals and TLR agonists. The existing literature clearly shows that chemical allergens can mobilize specific signaling pathways. Nickel and DNCB can rapidly activate mitogen-activated protein kinases (MAPKs) in human DC known to be highly involved in costimulatory molecule expression and cytokine production (Aiba *et al.*, 2003; Antonios *et al.*, 2009; Boislève *et al.*, 2004, 2005). Nuclear factor-kappa B (NF- κ B) is another transcription factor shown to be activated by numerous chemical sensitizers and implicated in the DC maturation process (Ade *et al.*, 2007; Antonios *et al.*, 2009, 2010; Neves *et al.*, 2011). A very interesting and new observation is that chemical sensitizers can activate upstream kinases such as CK2 (casein kinase 2), PKC (protein kinase C) or Syk (spleen tyrosine kinase). Using a peptide array approach, nickel and DNCB have been found to activate CK2 in DCs and inhibition of its activity altered DCs phenotype in response to these chemicals (de Bourayne *et al.*, 2017). Interestingly, CK2 activity can regulate pro-inflammatory cytokines production in DCs leading to Th1 cells polarization (de Bourayne *et al.*, 2016). PKC was initially shown to be involved in DC migration from the epidermis in response to TNCB and recent data suggested that PKC- β was essential for PPD and DNCB-induced CD86 expression in human DCs (Corsini *et al.*, 2014). Furthermore, chemical allergens such as 2,4,6 trinitrobenzene sulfonic acid (TNBS) and fluorescein isothiocyanate can activate Syk in DCs leading to pro-IL1 β synthesis (Yasukawa *et al.*, 2014). Recently, Lopez *et al.* showed in mo-DCs from amoxicillin (AX)-delayed allergic patients that MAPKs and NF- κ B, the main signaling pathways involved in DC maturation, were involved in Amoxicillin (AX)-induced DC phenotype modifications (Lopez *et al.*, 2015).

How can chemical sensitizers be “recognized” by DCs? Metals such as nickel and cobalt can bind to the imidazole groups of two histidine residues (His456 and His458) of the human TLR4. These metals and palladium were recently shown to potentially activate DCs via the TLR4 pathway (Rachmawati *et al.*, 2013; Raghavan *et al.*, 2012; Schmidt *et al.*, 2010; Schmidt and Goebeler, 2015). These histidine residues are absent in mice explaining why nickel is a poor sensitizer in mice and leading to the question of the relevance of these differences across species (Schmidt *et al.*, 2010). Gold can cause a modest DCs maturation depending on the TLR3 pathway (Rachmawati *et al.*, 2015). On the other hand, organic contact sensitizers can induce reactive oxygen species (ROS) production in human DCs (Byamba *et al.*, 2010; Corsini *et al.*, 2013), and this was linked to intracellular signaling (Neves *et al.*, 2011; Corsini *et al.*, 2013). ROS production is believed to act as second messengers mediating cellular responses and leading to immune cell activation (Kaplan *et al.*, 2012; Martin, 2012; Martin *et al.*, 2011). Adding the antioxidant N-acetyl-L-cysteine decreases p38MAPK phosphorylation and CD86 expression in response to contact sensitizers (DNCB, thiomersal) in DCs (Neves *et al.*, 2011). Moreover, using a proteomic approach, cinn and DNCB upregulated many proteins involved in oxidative stress (Mussotter *et al.*, 2016). Furthermore, TNBS (Yasukawa *et al.*, 2014), nickel (Li and Zhong, 2014), and chromium (VI) (Adam *et al.*, 2017) activated NLRP3 inflammasome via ROS production leading to caspase-1 activation and IL-1 β production. 2,4-dinitrofluorobenzene triggers, in a ROS-dependent manner, the activation of the PERK-eIF α -ATF4 unfolded protein response (UPR) branch and thus modulates human monocytic leukemia cells (THP-1) phenotype suggesting a link between ROS production, endoplasmic reticulum, and activation of UPR in chemical-induced inflammation (Luís *et al.*, 2014).

In resume, the hypothesis number 1 “Can haptens directly activate DC and play the role of danger signals?” is fully supported by the literature and it is now admitted that chemical sensitizers and some drugs following the hapten/prohapten concept can directly activate DCs in vitro through activation of specific signaling pathways leading to their maturation. Direct activation of DCs can be mediated either by specific recognition through TLRs in the case of some metals or by cellular stress leading to the activation of specific signaling pathways.

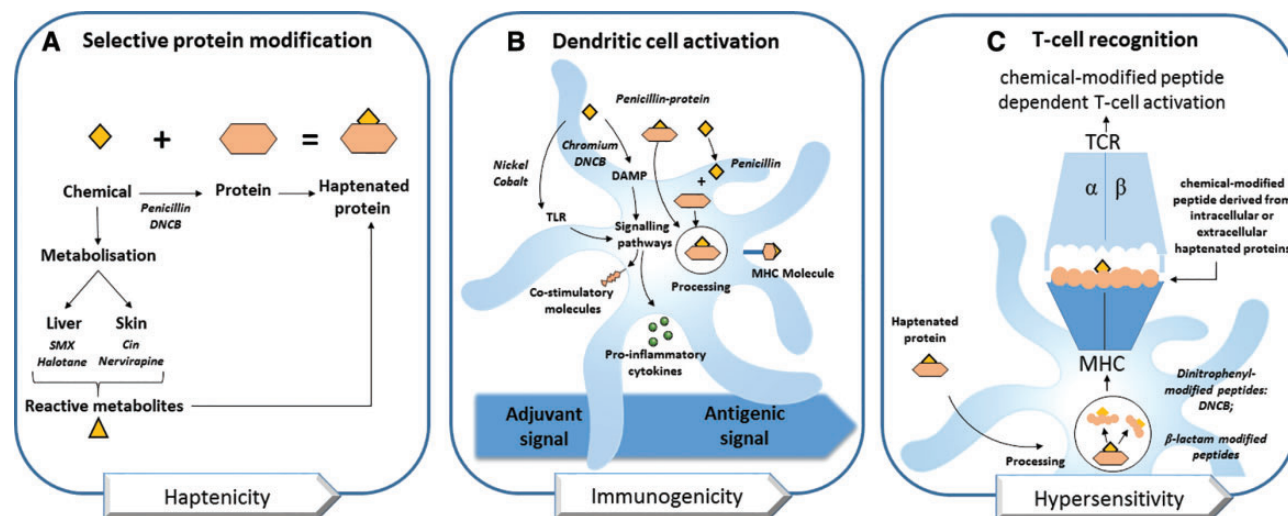


Figure 1. Chemical or drug allergy perceived as a true immune response. (A) Chemically reactive molecules or their metabolites can bind covalently and in a selective manner to self-proteins forming hapten-protein complexes. (B) The hapten-protein complex is then internalized and processed in dendritic cells leading to antigen formation. Chemicals or drugs can also bind to intracellular proteins in antigen-presenting cells. Some chemicals can also provide danger signals to dendritic cells through a direct or indirect mechanism that lead to costimulatory molecules expression and cytokine production. Both signals 1 and 2 are required for immunogenicity and effective T-cell priming. (C) T-cell receptor (TCR) recognizing peptide-chemical complexes may exist and pre-existing naive T-cell repertoire for some chemicals/drugs exist. TCR recognizes the hapten/self-peptide complex derived from the haptenated self-protein. Abbreviations: Cin, cinnamaldehyde; DAMP, damage-associated molecule patterns; DNCB, dinitrochlorobenzene; MHC, major histocompatibility complex; SMX: sulfamethoxazole.

Hypothesis 2: Can haptens modify the cellular microenvironment providing danger signals to dendritic cells?

The hypothesis that chemical allergens can indirectly activate DCs through modification of the microenvironment leading to generation of danger signals came from a striking observation that some contact allergens such as TNCB cannot induce a complete DC maturation in vitro (Martin et al., 2008). In fact, TNCB-treated DCs upregulated costimulatory molecules, in vitro, but did not trigger cytokine production (Martin et al., 2008). The observation that TNCB failed to induce contact dermatitis in mice lacking TLR2 and TLR4 but not in wild-type mice or even germ-free mice illustrated, one more time, the importance of TLR in contact dermatitis and strongly suggested that chemical sensitizers can induce the production of endogenous activators of PRR (DAMP) in the skin (Esser et al., 2012; Kaplan et al., 2012; Martin et al., 2008; Tsan and Gao, 2004). Indeed, chemical allergens were found to trigger oxidative stress, glutathione status perturbation (Schmidt and Chung, 1993), ROS production in the skin (Esser et al., 2012; Galbiati et al., 2014; Onami et al., 2014; Vandebriel et al., 2010; Wang et al., 2010) and also the release of low MWHA (Esser et al., 2012; Kavasi et al., 2017; Nikitovic et al., 2015), ATP (Onami et al., 2014) and HMGB1 (Galbiati et al., 2014) in vivo. Low MWHA can activate DCs through TLR2 and TLR4 (Scheibner et al., 2006; Termeer et al., 2002) and blocking hyaluronidase (HYAL) function, responsible for high MWHA degradation into low MWHA, prior to sensitization significantly reduced contact dermatitis in response to TNCB (Martin et al., 2008). The increase in the skin HYAL activity in mice is mediated by ROS and p38MAPK-dependent mechanisms (Esser et al., 2012). DNCB and PPD enhanced hyaluronan, an unsulfated glycosaminoglycan, degradation in keratinocytes leading to IL-18 production via oxidative stress (Nikitovic et al., 2015). Constitutive overexpressing of human HYAL1 in mice skin resulted in an increase in low MWHA release and exacerbated contact dermatitis (Muto et al., 2014).

ATP, released by stressed and damaged cells, can modulate immune responses through the transmembrane purinergic receptor P2X7 leading to NLRP3 inflammasome activation and IL-1 and IL-18 production (Kaplan et al., 2012; Watanabe et al., 2007). TNCB can trigger ATP release from skin mice in vivo and P2X7-deficient mice are resistant to contact dermatitis (Weber et al., 2010). Recently, it has been found that non-metal contact sensitizers induced ATP release from keratinocytes via ROS-mediated opening of pannexin 1 hemichannels (Onami et al., 2014).

HMGB-1, a TLR4 agonist, is also released into the extracellular environment by damaged cells. Contact sensitizers can induce the release of HMGB-1 from keratinocytes provoking IL-18 production via a TLR-4-dependent mechanism (Galbiati et al., 2014).

In resume, the hypothesis number 2 “Can haptens modify the cellular microenvironment providing danger signals to DCs?” is supported by recent reports showing that increase in skin ROS production by chemical sensitizer is the key for triggering in situ release of soluble factors known to be involved in the creation of a danger environment. This danger environment can modify the epimicrobiome leading to an effector immune response to environmental chemicals.

CHEMICAL OR DRUG HYPERSENSITIVITY: A TRUE IMMUNE RESPONSE WITH THE IMMUNE SYSTEM BEING TRIGGERED FOR ITS ROLE THAT IS CLEARING A DANGER OR AN ACCIDENT WITH UNCONTROLLED CONSEQUENCES LEADING TO IMMUNOPATHOLOGY?

Living organisms are constantly exposed to environmental products including chemicals. In such, detoxification mechanisms have evolved allowing survival of these living organisms in a stressed environment. The immune system is a host defense system protecting against disease and must detect a

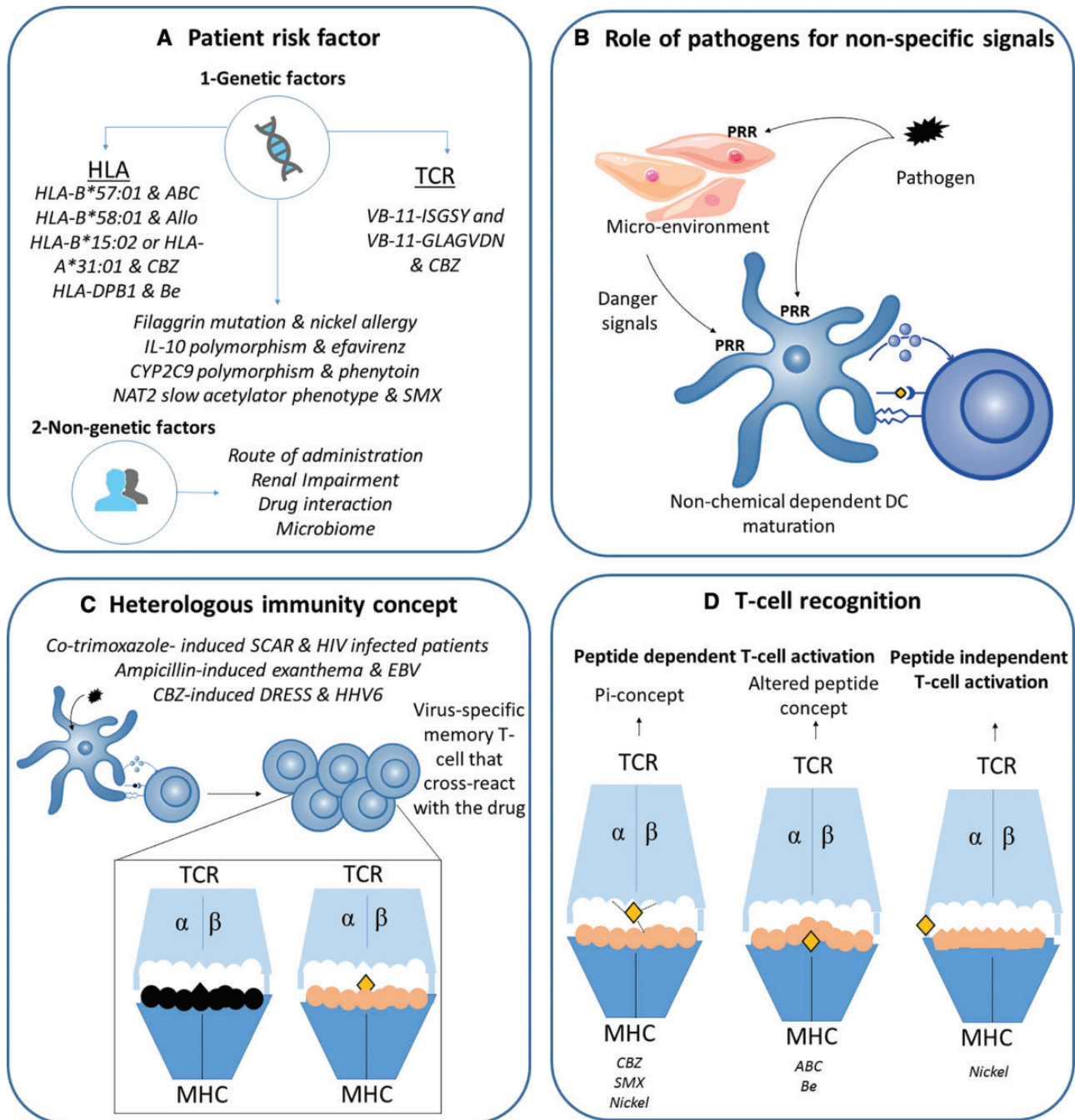


Figure 2. Chemical or drug hypersensitivity perceived as an accident with uncontrolled consequences leading to immunopathology. (A) Chemical/drug-induced allergic reactions may depend on patient risk factors such as genetic factors or non-genetic factors related to the drug formula, dosage, administration, or presence of a concomitant disease. (B) Pathogens can deliver the adjuvant signal needed for dendritic cell (DC) modifications and efficient T-cell priming independently of the chemical/drug. (C) Moreover, unrelated antigens can bind to the same T-cell receptor (TCR) as proposed by the heterologous immunity concept. Virus-specific memory T cells that were generated during a previous infection may cross-react with the chemical or the drug. (D) Chemicals or drugs can bind accidentally to the TCR or to HLA molecules outside of the antigen-binding groove through non-covalent interactions (pi-concept). Other chemicals or drugs can bind accidentally within the antigen-binding groove of specific HLA molecules altering the repertoire of endogenous peptide ligands presented by this major histocompatibility complex (MHC) (abacavir [ABC]). Other chemicals can activate the TCR accidentally with the correct MHC haplotype, but independently of any peptide. Abbreviations: Allo, allopurinol; Be, beryllium; CBZ, carbamazepine; CYP, cytochrome P; NAT2: N-acetyltransferase 2; PRR, pattern recognition receptor; SCAR, severe cutaneous adverse drug reactions; SMX, sulfamethoxazole.

wide variety of agents and distinguish them from the organism's own healthy tissue. Consequently, the immune system is as a protective system avoiding dangerous pathogens to develop in the infected organism. Disorders of the immune system can result in autoimmune diseases, inflammatory diseases,

infections and cancer. Autoimmunity results from a hyperactive immune system attacking normal tissues as if they were foreign organisms. In this instance, dysfunction in regulatory mechanisms are at the origin of these diseases. Hypersensitivity is an immune response that damages the body's own tissues and it is

the consequence of exposure to foreign antigens. However, is hypersensitivity an accident resulting in an uncontrolled immune response to foreign antigens or does hypersensitivity have a role in protecting living organism from environmental triggers including reactive chemicals?

Concerning chemical and drug allergy, three models describing how small molecules can elicit T-cell reactivity leading to hypersensitivity reactions are proposed: the hapten/prohapten model, the pharmacological interaction model (p-i), and the altered peptide repertoire model. In the hapten/prohapten model, chemical reactivity is the key step for a chemical to be an allergen leading to clinical manifestations. It allows chemicals to bind to proteins and to deliver danger signals to DCs leading to their maturation. Indeed, chemical allergens have found very specific ways to activate the immune system through TLR activation or modification of the cellular microenvironment at the site of exposure. Furthermore, chemical-protein complexes are processed and specifically associated to HLA peptides (Martin *et al.*, 2010). When presented in the context of MHC, these modified peptides will be recognized as “foreign” by T cells eliciting a “true immune response” directed to the peptide-chemical complex; this immune response can also involve B cells (Amali *et al.*, 2017). The multiplicity of binding sites on proteins generated by these chemicals expand the repertoire of haptenized peptides to be recognized by T cells and consequently no strict HLA association has been described in this context. This latter mechanism concern many people strongly suggesting a true immune response directed to a reactive foreign entity possessing the likely characteristics of a harmful chemical. In light of these observations, hypersensitivity reactions are supported by a specific immune response and could be considered as a defense mechanism avoiding prolonged exposure to dangerous reactive chemicals (Figure 1).

On the other hand, there are cases where the incidence of allergy to a product is very low suggesting that specific conditions associated with the patients or the environment (genetic factors, viral infections, health status, etc) need to be present (Figure 2A and 2B). Interestingly, priming of naive T cells failed for some chemicals in healthy donors (Faulkner *et al.*, 2016; Gibson *et al.*, 2015), illustrating the presence of individual predisposition factors that could promote sensitization independently of specific T cells. Some hypersensitivity reactions are mainly associated with genetic susceptibility (ie, filaggrin mutation) (Kezic, 2011) and MHC molecules (Falta *et al.*, 2013; Usui and Naisbitt, 2017). The case of abacavir, a guanosine analog inhibiting HIV-1 reverse transcriptase enzyme, is at the origin of the “altered peptide repertoire model” where the drug occupies a position in the peptide-binding groove of the MHC protein changing the peptide specificity of the MHC binding. The abacavir hypersensitivity syndrome occurs exclusively in patients carrying the HLA-B57*01 allele suggesting that abacavir allergy is an accident concerning a very restricted number of people (Figure 2D). Moreover, the allo-immune stimulation provided by the abacavir-peptide-HLA B57:01 complex is stimulatory enough without need of “danger” as a cofactor reinforcing the unique feature of abacavir allergy. In other cases, a nonspecific inflammation independent of chemical exposure can be sufficient to provide necessary danger signals provoking an effector immune response to a bystander antigen present at the site of inflammation. In this case, chemical-protein complexes are the bystander antigens processed by DCs, thus, creating haptenized peptides presented to T cells (Figure 2B). Recently, some T cell-

mediated hypersensitivity reactions have been described to represent a good example of heterologous immunity (4). In this model, cross-reactive T-cell responses stem from activation of pathogen-specific memory T cells that recognize the neoantigen created by drug exposure; to this extent, HHVs are a likely source of persistent antigens (Figure 2C).

Particular features of chemical and drug hypersensitivity are the diverse mechanisms of T cell activation (Figure 2D). Chemicals, mostly metals, can bind to peptides already present in the HLA pocket or modify the structure of these pockets, creating new antigens (self-modified) (Falta *et al.*, 2013; Thierse *et al.*, 2005). The p-i concept has emerged over the past 2 decades and describes situations where drugs can stimulate T cells via noncovalent direct interaction with T-cell receptor (TCR) and/or peptide-MHC complex (Pichler and Hausmann, 2016). In the p-i TCR the drug fits into some of the different TCR available. Sulfamethoxazole interacts with the CDR3 regions of the TCR, which usually interacts with the peptide-HLA complex. In p-i HLA the drug binds directly to the HLA molecule (Pichler and Hausmann, 2016). For these latter situations, it can be hypothesized that due to coincidence, the drug binds to the CDR3 region of the TCR or to the HLA molecule, and due to particular situations, this may be at the origin of the drug-induced hypersensitivity.

CONCLUSION

Chemical or drug allergy may be the consequence of different key steps that allow DCs to prompt an adaptive immune system. Despite the presence of numerous chemical sensitizers, extremely diverse in weight and structure, most of them share a particular feature: “chemical stress.” In fact, intrinsic protein reactivity (or after their oxidation/metabolism), mainly electrophilicity, is important for protein haptenation allowing chemical allergens to become immunogenic. Moreover, chemical reactivity can be translated into an activation of the innate immune system and a biological response. Our hypothesis is that allergic reactions involving drug or chemical specific T cells are the consequences of a biological determinism that has developed to protect living organisms eliminating dangerous chemicals provoking acute or chronic toxicity.

However, in some rare cases, hypersensitivity reactions can be an accident due to genetic predispositions or specific features of the molecule of concern. In these situations, the immune system is fooled by drugs or chemicals leading to immunopathological reactions mostly mediated by T cells.

Questions are also still open concerning specific T cell repertoires for chemicals and drugs. Due to the artificial nature of chemical-T cell epitopes, it is not clear whether the selection of chemical-specific T cells is a common phenomenon or remains limited to few donors. A large T cell repertoire found in multiple donors would underline the potential of chemical to be recognized by many donors accounting for the “protective” and “detoxication” effect of the immune system.

Nevertheless, more research is needed to understand the mechanisms allowing the translation from the sensitization phase to the allergic reaction. What are the mechanisms dictating the fate of the response from sensitization, controlled by immune tolerance, to immunopathology? Can the situations in which the immune system is fooled generate an immunological memory?

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