Allergology International 74 (2025) 33–41

Contents lists available at ScienceDirect

Allergology International

journal homepage: http://www.elsevier.com/locate/alit

Review Article

Delayed drug hypersensitivity reactions: How p-i transforms pharmacology into immunology

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ARTICLE INFO

Article history:
Received 3 July 2024
Received in revised form
9 August 2024
Accepted 14 August 2024
Available online 17 September 2024

Keywords:
Alloreactivity
Cytotoxicity
Drug hypersensitivity
Eosinophilia
p-i mechanism

Abbreviations:
AGEP, acute generalized exanthematous pustulosis; DC, dendritic cells; DH, drug hypersensitivity; dDHR, delayed appearing drug hypersensitivity; DReSS, drug rash/reaction with eosinophilia and systemic symptoms; LN, lymph nodes; MDH, multiple drug hypersensitivity; MPE, maculopapular exanthema; p-i, *p*harmacological interaction with *i*mmune receptors; SJS/TEN, Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis; TARC, thymus and activation related chemokine; TCC, T cell clones; TSLP, thymic stromal lymphopoietin

ABSTRACT

Delayed drug hypersensitivity reactions (dDHRs) are iatrogenic diseases, which are mostly due to non-covalent interactions of a drug with the immune receptors HLA and/or TCR causing T-cell activation. This is also known as pharmacological interaction with immune receptors or p-i. P-i activation differs from classical antigen-driven immune reactions: a) drug binding induces structural changes in TCR-HLA proteins which make them look like allo-like TCR-HLA-complexes, able to elicit allo-like stimulations of T cells with cytotoxicity and IFNγ production, notably without the involvement of innate immunity; b) drug binding to TCR and/or HLA can increase the affinity of TCR-HLA interactions, which may affect signaling and IL-5 production by CD4+ T cells, and thus contribute to eosinophilia commonly found in dDHRs or induce oligoclonal T cell expansions; c) Both, antigen and p-i stimulations can induce eosinophil- or neutrophil-rich inflammations; but these stimulations should be distinguished as their underlying mechanism and development differ; and d) p-i stimulation can – like graft versus host reactions – result in long-lasting T-cell activations, which can lead to viremia, occasional autoimmunity, or a new syndrome characterized by multiple drug hypersensitivity (MDH).

In summary, dDHRs are not allergic reactions but represent peculiar T-cell activations, similar to allo-like stimulations. Understanding and considering the p-i mechanism is needed for preventive measures and optimal treatments of dDHR. In addition, it may help to understand TCR signaling, alloreactivity, and may even open a new way of specific immune stimulations.

Introduction to delayed drug hypersensitivity: p-i bridges pharmacology with immunology

DHRs are modern, iatrogenic diseases that are difficult to manage and investigate, as they appear unexpectedly, are transient, and have rarely been empirically validated in animal models.[1,2] Drug hypersensitivity reactions (DHRs) range from acute onset DHR, such as urticaria and anaphylaxis, to delayed-onset DHR (dDHR), such as macular or maculopapular exanthem (MPE), Drug Reaction with Eosinophilia and Systemic Symptoms (DReSS instead of DRESS, as eosinophilia is found in only approximately 75% of cases), Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), and Acute Generalized Exanthematous Pustulosis (AGEP).[1,2]

Initially, DHRs were considered antigen-driven immune activations,[3] in which a stable hapten-protein complex serves as a new antigen. However, due to the absence of co-stimulation, the immune system overlooks most hapten-induced neoantigens.[4,5] Further extensive analysis of immune responses to drugs in patients with dDHRs revealed that most T-cell activation originates from an alternative pathway. It involves the off-target activity of a drug with immune receptors, such as Human Leukocyte Antigen (HLA) and/or T-cell receptor (TCR), leading to T-cell activation. This process is termed "pharmacological interaction with **i**mmune receptors" or "p-i".[1,2,6,7] Multiple p-i stimulations that result in

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https://doi.org/10.1016/j.alit.2024.08.006

different functional outcomes can occur simultaneously and are collectively referred to as a "p-i concept".[8]

The initiation of an immune response is a complex, highly regulated process. It is thus surprising that drug binding to immune receptors can trigger complex responses such as dDHR. But there are other examples of strong T-cell stimulation, like superantigen or direct allo-stimulation, where strong immune reactions occur without antigen processing and bypassing innate immunity involvement.[9–11] P-i stimulation and dDHR represent another of these unorthodox, alternative forms of T-cell stimulation.

Elucidating DHR pathways: the role of hapten and p-i stimulation

Although drugs are typically too small to directly serve as antigens, they can initiate a specific immune response and elicit DHR by binding to proteins through two primary mechanisms (Fig. 1):

a) Drugs primarily bind to proteins non-covalently. These labile interactions depend on electrostatic interactions, hydrogen bonds, and van der Waals forces and are mostly irrelevant to the immune system. However, some drugs (e.g., β-lactams) can also bind covalently to a protein, following an initial non-covalent binding.[5] These drugs are called haptens and can form a stable hapten-protein complex, which can function as a new antigen and elicit drug-specific antibodies and T-cell reactions. These new antigens are abundantly present after, for instance, therapy with β-lactams but are typically ignored by the immune system owing to the lack of co-stimulation.[4,5] However, if hapten formation occurs on proteins of already activated tissue cells, such as during concomitant viral infection, immune reactions with clinical symptoms such as exanthem may develop (Fig. 1).[12] The coincidence between viral infection and antibiotic therapy is the leading cause of drug-related exanthems in childhood.

b) Some non-covalent drug–protein binding may become relevant for the immune system if it targets immune receptors such as HLA and/or αβTCR.[6,7] The specific role of drug binding to other receptors, such as NK-R or γδTCR, and non-classical HLA molecules has not yet been explored. Various drug-binding sites on the HLA structure have been identified through crystallography and modeling, resulting in their designation as p-i-HLA.[6,13–17] Various forms of p-i-TCR exist, which differ based on the region (e.g., CDR3α, or CDR2β) affected by the drug (Fig. 2).[18–20] This interaction has typical features of a pharmacological interaction, as evidenced by the identification of various activating and inhibitory sulfanilamides[21] that target the TCR region.

The potential of drug binding (p-i) may depend on its relevance to signaling (TCR) or presentation (HLA) (Fig. 2).[6] It may elicit massive cell expansion (DReSS) or predominant cytotoxicity and severe cutaneous adverse reactions, such as SJS/TEN.[22,23] Similarly, p-i stimulation can be enhanced by concomitant immune stimulation, such as viral infections with high levels of interferon-gamma

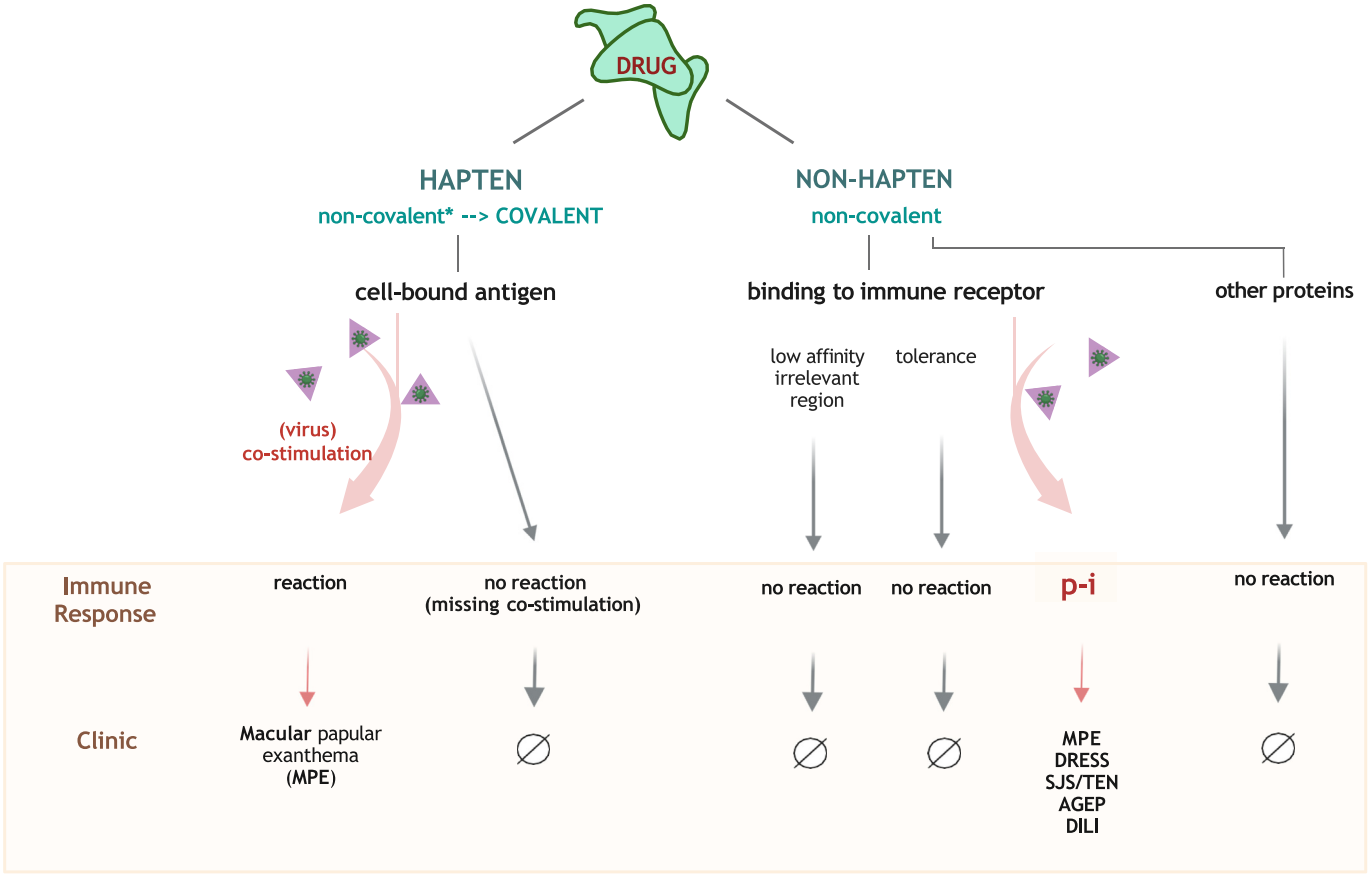

Fig. 1. Drug Interaction with Immune System: antigen formation or pharmacological interaction (p–i). Hapten and non-Hapten drugs. Hapten drugs, such as β-lactams, can form a new antigen by binding covalently to proteins. However, the immune system tends to ignore these new antigens as co-stimulation is lacking.[4,5] If these new antigens are formed on already activated cells, e.g. during a generalized virus infection, co-stimulation is provided by the virus induced immune reaction, and a dDHR may occur (mostly MPE).[12] Non-covalent binding (labile, reversible) of drugs to proteins is mainly irrelevant to the immune system. However, if drug binding happens to occur to an immune receptor (TCR or HLA), it can induce an immune reaction.[5–7] Generally, this binding is characterized by low affinity or occurs on a part of the immune receptor, which does not elicit functional consequences. In addition, tolerance mechanisms often block T-cell activation. Some of the drug binding may be affine enough and occurs to relevant parts of the immune receptors, which then can elicit a T cell reaction: p-i stimulation and a dDHR may evolve. Virus infection can amplify the p-i reaction.[12] The details of the p-i interaction are shown in Figure 2.

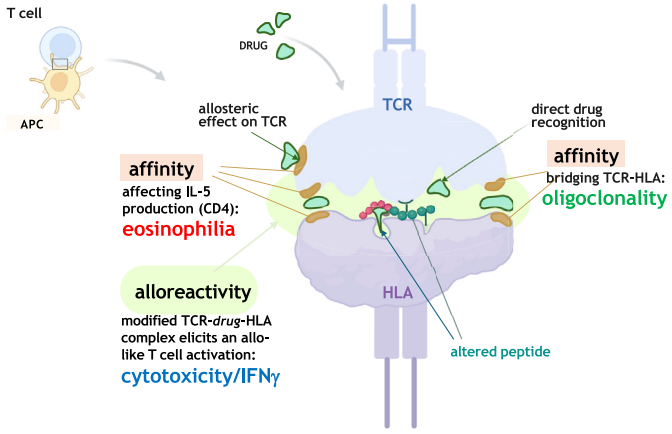

Fig. 2. P–i: transformation of off-target drug activity into complex immune response. Drug binding to immune receptors (TCR or HLA) has distinct functional consequences, depending on the binding site. The drug-binding can increase the affinity of TCR↔HLA:
- Sulfamethoxazole binding to TCRVβ2 may exert an allosteric effect on the TCR, which results in an 7-fold increased affinity of TCR to HLA/peptide.[18].
- The drug may link HLA and TCR in such a way that an oligoclonal expansion of T cells occurs[19,20,50]
- The drug may bind to the TCRVβ1.[21] In this constellation, some drug reactive T cell clones can become activated even if HLA-mismatched antigen presenting cells are involved (shown for sulfamethoxazole, lidocaine; 44).
The dominant effect of drug binding to TCR/HLA is an *allo-like stimulation* eliciting cytotoxic activity (perforin, granzyme B, granulysin, FasL) and IFNγ secretion by the T cell. Different binding sites on HLA-proteins can lead to such activities, but drug binding to TCR itself can also lead to allo-like stimulations (13–17, 43 and own data with sulfamethoxazole specific TCC).

(IFNγ), which increases the number of immune receptors and thus the number of p-i-modifiable TCR/HLA molecules.[12]

Risk alleles and drugs may be sufficient to induce in vitro reactivity to the drug but not in vivo. All abacavir-naïve 57:01+ peripheral blood cells, when incubated with abacavir for 14 days in vitro, developed IFNγ-secreting and cytotoxic CD8+ T cells.[24] However, only 54% of the treated B*57:01+ individuals developed a reaction to abacavir in vivo.[25] The disparity between the presence of risk allele, drug exposure, and the emergence of disease is even more pronounced in other HLA-allele-linked DHRs (carbamazepine, allopurinol, vancomycin, dapsone, flucloxacillin, sulfasalazine, etc.).[15–17,26–28] Various suppressor mechanisms appear to prevent clinical manifestations even when both drugs and risk alleles are present.[29–31]

Conclusion and clinical impact: Most drugs acting as haptens or via p-i are well tolerated due to the lack of co-stimulation and the presence of a potent suppressor mechanism that prevents reactivity. The manifestation of dDHR is often associated with concomitant viral infection or increased dosage. Re-exposure without co-stimulation is mostly tolerated, particularly in cases of originally mild childhood antibiotic exanthemas. Exceptions may be severe dDHRs, which can recur upon re-exposure without viral co-stimulation. Such patients exhibit persistent strong skin tests (patch or id) or in vitro reactivity to β-lactams (own observation).

The p-i concept as a unifying explanation for most dDHRs

Numerous studies have investigated non-covalent drug binding to immune receptors and their effects on T-cell stimulation. Some include unorthodox immune stimulations by drugs, such as CD4 T-cell interactions with HLA class I or CD8 with HLA class II.[32,33] Many of these non-covalent interactions with immune receptors – particularly those binding to HLA - were not classified as p-i. But they all share the common characteristic of p-i, namely "non-covalent drug binding to immune receptors with functional consequences." This indicates that a unifying "p-i concept" can explain most forms of dDHR and their mechanism.[5,6]

One of the major obstacles to the acceptance of the p-i concept is the difficulty in demonstrating it. The p-i concept is based on the analysis of drug-specific T-cell clones (TCC), which were initially expanded in cell culture for 6–8 weeks, a process pursued in only a limited number of laboratories.[32–37] The analysis revealed an immediate reaction to the drug before antigen processing and presentation. Complete T-cell stimulation requires the presence of antigen-presenting cells (APCs), but blocking of processing or metabolism did not prevent T-cell reactivity to drugs.[34,35]

Although the clinical relevance of p-i for dDHR was unclear when it was first described,[34,35] it is currently recognized as the *primary pathway responsible* for eliciting dDHR: the arguments are summarized in Table 1.

Conclusion and clinical impact: Severe dDHR, such as DReSS, SJS/TEN, AGEP, and many MPE are due to p-i. The presence of eosinophilia in DHR suggests the involvement of p-i.[8] Some drugs can act via p-i or hapten, whereby the more severe reactions are associated with p-i.[38,39] As reported recently, also the presence of immune complex deposits in the milder hapten reactions may help to differentiate them from more severe p-i mediated dDHR.[40]

The unique pathway of p-i: transforming pharmacology into immunology

In p-i, an off-target drug activity is transformed into a complex immune response (Fig 2). Drug binding creates an allo-like configuration of the TCR-drug-HLA complex and/or a higher affinity for TCR-HLA interactions (Table 2).

P-i mechanism/involvement of drug/{TCR-HLA} interactions. For full T-cell activation by p-i, an interaction between TCR-expressing

Table 1
P-i stimulations are the main cause of dDHR (severe MPE, DReSS, SJS/TEN, AGEP).

Category	Detail	References
Dominance of p-i mechanism in severe dDHR	Most drug-specific T-cell lines/clones in severe MPE, DRESS, SJS/TEN, and AGEP are stimulated by the p-i mechanism. MPE can be due to p-i or hapten mechanisms.	15–17,32,33,36,37,44,50
HLA associations with p-i	Drugs bind non-covalently to HLA structure, some even exclusively to specific alleles, explaining HLA associations in severe dDHR.	13–17,26–28
Oligoclonal T-cell expansions	Seen in SJS/TEN and some DReSS due to direct drug interaction with TCR, indicating the p-i mechanism.	19,20,50
Eosinophilia as a sign of p-i mechanism	Presumably linked to enhanced TCR-HLA affinity, it occurs in ~50% MPE, ~75% DReSS, and ~25% AGEP patients. Some p-i mediated dDHR lack eosinophilia (e.g., abacavir-induced DHR).	8
Drugs causing dDHR without antibody reactions	Some drugs like antiepileptics (lamotrigine, phenytoin, carbamazepine) and antibiotics (clindamycin, vancomycin) can act only via p-i or pseudo-allergy (vancomycin): No hapten features, and no IgE or IgG reactions are present; only in mild dDHR due to hapten mechanism, immune complex deposits are found	1,40
Drugs acting via p-i or as a hapten	Some drugs, including β-lactams and PPIs, stimulate T cells via hapten or p-i mechanisms. Comparisons show that p-i is linked to severe reactions (DRESS, hepatitis) and haptens to milder reactions (MPE).	38–40

Table 2
A unifying concept for dDHR: p-i - transforming pharmacology into immunology.

P-i mechanism	Details
1) Pharmacology: off target binding to TCR &/or HLA	The drug binds to TCR or HLA (or both); p-i stimulation occurs when **both receptors/both cells interact** (TCR-HLA complex)
2) Immunology: Functional consequence of p-i	Transformation of a pharmacological signal into **immune effector function**, always occurring in reactive T cells.
2a) *Change of TCR-HLA struc- tures: allo-like stimulation*	Changing the protein-structure of immune receptors (HLA and TCR) by drug-binding unleashes the power of **alloreactivity** (cytotoxicity, IFNγ↑)
2b) *drug binding affect TCR↔HLA affinity*	Some drug binding/p-i can enhance the affinity of TCR↔HLA interactions, affecting **cytokine production** (IL-5↑ in CD4+) or **oligoclonal** T cell expansion (CD8, CD4)

T cells and HLA-expressing tissue cell/APC is required.[34,35] This two-receptor/two-cell interaction sets p-i apart from other off-target activities of drugs because the effects of p-i are not restricted to the cell to which the drug binds. Consequently, p-i always stimulates T cells, even if the drug first binds to HLA in tissue cells.

Functional consequence of p-i: transforming pharmacology into immunology. The binding of the drug to TCR or HLA is considered a *pharmacological, "off-target"* action. It leads to the formation of a {TCR-drug-peptide-HLA} complex, which triggers a signal in T cells (p→i), ultimately resulting in *immunological* activity. However, the specifics of TCR/CDR3 signaling in T cells have not yet been elucidated.[41,42] A possible connection between the drug-binding region of the TCR–HLA complex and its function is shown in Figure 2.

Alloreactivity arises when drug binding alters the *structural proteins* of HLA and TCR, marking a decisive difference from traditional antigen/hapten-protein reactions where an altered, *immunogenic peptide* (hapten-peptide) is presented after processing, leaving HLA and TCR proteins unchanged.[3] However, in p-i, the drug modifies the structural proteins, leading to one of the most potent immune stimulations, known as direct alloreactivity.[6,10]

An instructive example linking DHR with alloreactivity is abacavir hypersensitivity: The interaction of abacavir with HLA-B*57:01 mimics B*58:01, causing 5% of abacavir-induced TCC to react with both forms, demonstrating that the drug-induced reactivity is identical to its alloreactivity against HLA-B*58:01.[43] Alloreactivity is also more prevalent in drug-specific TCC than in peptide-specific ones.[44]

P-i-activated T cells function similarly to allo-activated T cells, as they can be stimulated without DC co-stimulation, bypassing innate immunity and activating naïve and memory T cells directly.[6,43] Allo-stimulation results in cytotoxicity mediated by granzyme B, perforin, granulysin, FasL.[10,11,45–47] Cytotoxicity (and IFNγ production) is elicited when the drug binds to HLA (e.g., abacavir, carbamazepine, dapsone, vancomycin 13,14,24,33 or TCR (e.g., sulfamethoxazole, lidocaine).[19–21,34,35] As an interaction between TCR and HLA is required for effective immune stimulation,[34,35] this stimulation is best explained by an alteration of the entire HLA-TCR complex rather than by an isolated modified HLA or TCR (Fig. 2).

Cytotoxicity occurs in reactive CD8+ cells and is dominant in SJS/TEN.[23,47] However, in MPE, drug-reactive T cells are predominantly CD4+ and cytotoxic, where perforin+/CD4+ T cells are found near keratinocytes that undergo hydropic degeneration[48] (Fig. 3, 4). Indeed, cytotoxicity is the most characteristic feature of all forms of dDHR (MPE, AGEP, DReSS, and SJS/TEN).[46]

The potential connection between the induction of IFNγ-production and allo-stimulation or cytotoxicity is suggested by the fact that most peripheral cytotoxic T-cell clones (p-i TCC) exhibit both cytotoxicity and produce IFNγ.[32,33,49]

Increased TCR-HLA affinity, the second mechanism that alters signaling, can result from various p-i interactions enhancing TCR↔HLA affinity (Fig. 2): The drug might bind to TCR itself, eliciting an *allosteric* effect on the TCR2β, increasing affinity to the HLA-peptide complex.[18] Alternatively, drug binding could directly enhance TCR-HLA affinity, which makes CD4 co-stimulation not necessary.[32,33] This omission of CD4 co-stimulation could facilitate a unique IL-5-TCR signalosome, resulting in high IL-5 levels and subsequent eosinophilia.[8] A third way of increasing affinity may result in drug interactions with HLA and specific TCR regions, triggering monoclonal or oligoclonal T-cell stimulations, as seen in SJS/TEN.[19,20,50]

Altered peptide presentation: This model has only been described for abacavir. Abacavir can be presented by binding directly to the HLA-molecule on the cell surface, but also after drug uptake, reaching the endoplasmic reticulum and binding to the HLA allele (B × 57:01).[51] This may induce an allo-response.[13,44] In addition, the drug binding alters the peptide-binding capacity of the HLA molecule and an altered peptide repertoire is presented.[13,14,52] While the modified peptide loading for abacavir has been well-documented, it has not been shown whether the presentation of altered peptide induces peptide-specific T cells and autoimmunity.

Conclusion and clinical impact: Various p-i stimulations co-occur in dDHR, and differ from protein-antigen stimulations. Instead of Gell & Coombs (G&C) Type IV a,b,c,d, one might distinguish "p-i cytotox" and "p-i IL-5" (Fig. 4). "P-i cytotox" is due to a modified {TCR-drug-HLA} complex, which appears to be the driving force in nearly all dDHR (MPE, AGEP, DReSS, SJS/TEN). "P-i IL-5″ leads to eosinophilia, occurring in approximately 25% of AGEP, 50% of MPE, and 75% of DReSS patients.[8]

Classic versus) alternative T cell stimulation leading to inflammations

The development of inflammation, whether caused by antigens or by drugs/p-i is distinct.

Immune and inflammatory responses to pathogens or allergens are intricate processes that unfold stepwise.[53–55] For instance, in eosinophilic skin inflammation, allergens/antigens, and co-stimulatory molecules trigger the release of TARC, TSLP and possibly IL-33 by keratinocytes and macrophages. This activates ILC2, which then stimulates DCs and other cells, leading to the release of cytokines. DCs react to the costimulatory molecules, incorporate antigen/allergen proteins and migrate to the lymph node, presenting immunogenic epitopes and promoting Th0 to Th2 maturation. T cells then migrate to the affected tissue, where Th2 cells amplify and promote T2-biased inflammation. This process produces IL-4, IL-13, and IL-5, as well as eotaxin and TARC, which contribute to the recruitment and accumulation of eosinophils (Fig. 3).

The sequence of events in p-i is the inverse of antigen-driven reactions (Fig. 3). Drugs are distributed throughout the body in minutes. Most small molecular drugs are not antigens per se and do (in permitted, therapeutic concentrations) not cause co-stimulation/danger: there is no antigen processing, no priming of T cells by DC-derived cytokines and no Th1, Th2, and Th17

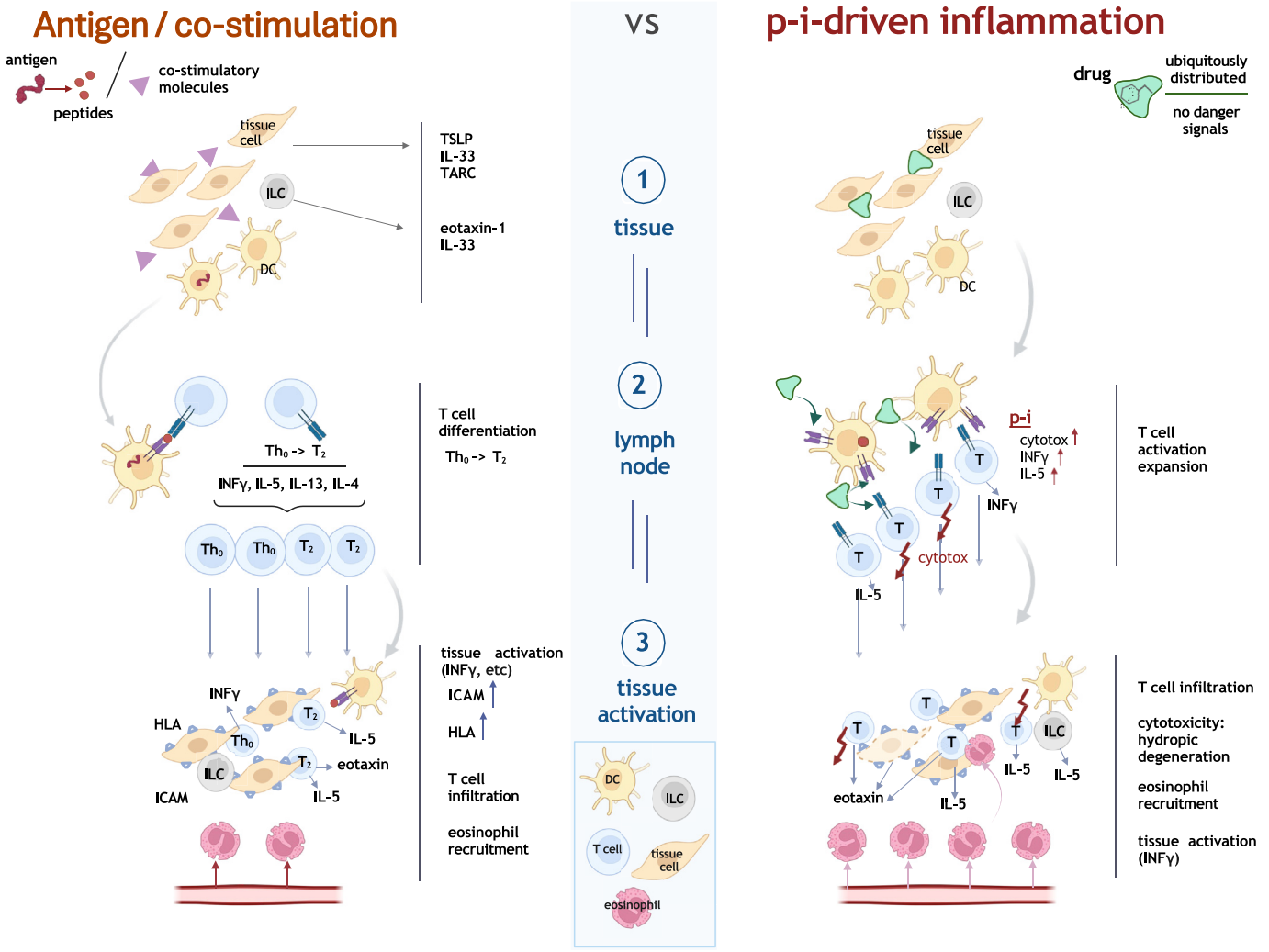

Fig. 3. Development of antigen/allergen-specific, co-stimulation-dependent T-cell immunity versus p-i stimulation of T cells in dDHR. Tissue cells are activated by antigens/allergens associated with co-stimulatory molecules to secrete IL-33, TARC, TSLP, etc,[53–55] which "alarm" tissue cells, innate immune cells (ILC) and DC. Dendritic cells (DC) internalize protein antigens, migrate to the lymph nodes (LN), and present antigenic peptides to T helper (Th) cells that differentiate into Th2 cells.[53] Th2 cells proliferate, migrate into tissues, secrete cytokines/chemokines and interact with tissue cells. Cytotoxicity is of minor importance. Eosinophils are recruited and activated by eotaxin and IL-5 secretion. In p-i-induced inflammation, the drug first activates some T cells close to APC in the lymph nodes; these T cells expand and migrate to the tissue (mostly the skin), where they re-encounter the drug. The p-i-activated T cells secrete IFNγ, which activates tissue cells/ILC/DC/monocytes and induces cytokines/chemokines such as eotaxin/IL-5 and the expression of HLA-II and ICAM, which – in MPE - facilitates interaction with CD4+ activated T cells.[48,56,57] Activated cells are cytotoxic ("p-i cytotox"), causing hydropic degeneration. In many dDHRs, some T cells are stimulated to secrete high levels of IL-5, which further attracts eosinophils ("p-i IL-5").

maturation. Even if the drug can act as haptens, the formation of a hapten-protein complex (neoantigen) takes time (hours) and remains unnoticed by the immune system, as co-stimulation is lacking (see above and Fig. 1;[4]).

Thus, a drug may cause immune stimulations only under special circumstances (e.g. sufficient affinity of the drug for the available immune receptors): thereby T cells are activated first, with lymph node (LN) swelling (MPE, DReSS), suggesting that p-i stimulation and T-cell replication begin in the LN, where the proximity of T cells and APC allows for off-target drug action and signal transmission through HLA-drug-TCR complexes. In other words, p-i stimulation occurs unexpectedly, bypassing the innate immune system and directly activating naïve and memory T-cells.[43] Specific suppressor mechanisms can inhibit T cell expansion.[29–32] Increasing the dose, prolonged treatment or viral infection may disrupt these inhibitory mechanisms, leading to "successful" p-i stimulation with T cell expansion, migration, and homing to the tissue (mainly the skin), where they re-encounter the drug. The peculiar mode of p-i stimulation make the T cells cytotoxic, which cause damage, such as hydropic degeneration of keratinocytes, which is the dominant histological feature of dDHR[56] (Fig 4). They also secrete cytokines like IFNγ, which can enhance expression of adhesion molecules, e.g., ICAM and HLA-class II on keratinocytes and monocytes. In many dDHR, IL-5 is produced by ILC and T cells, while tissue cells release TARC and eotaxin, all able to recruit eosinophils typical for dDHR.[57]

The clinical presentation of dDHR depends on the type of activation, which consistently includes cytotoxicity, frequently IFNγ, IL-5, and occasionally GM-CSF, IL-8, IL-36γ and others. P-i activation with the same drug can lead to different clinical manifestations and organ involvement, which remains an unresolved issue and warrants further investigation[58] (Fig. 2-4).

Atopic dermatitis (antigen-driven inflammation) and MPE/DReSS (p-i mechanism) show eosinophilic inflammation, both of which were assumed to represent T2 inflammation.[59] However, DReSS/severe MPE are not examples of T2-type inflammations because the cause (drug vs. antigen/co-stimulation) and sequence of events in classical/antigen- or p-i-induced inflammation are different (Fig. 3).

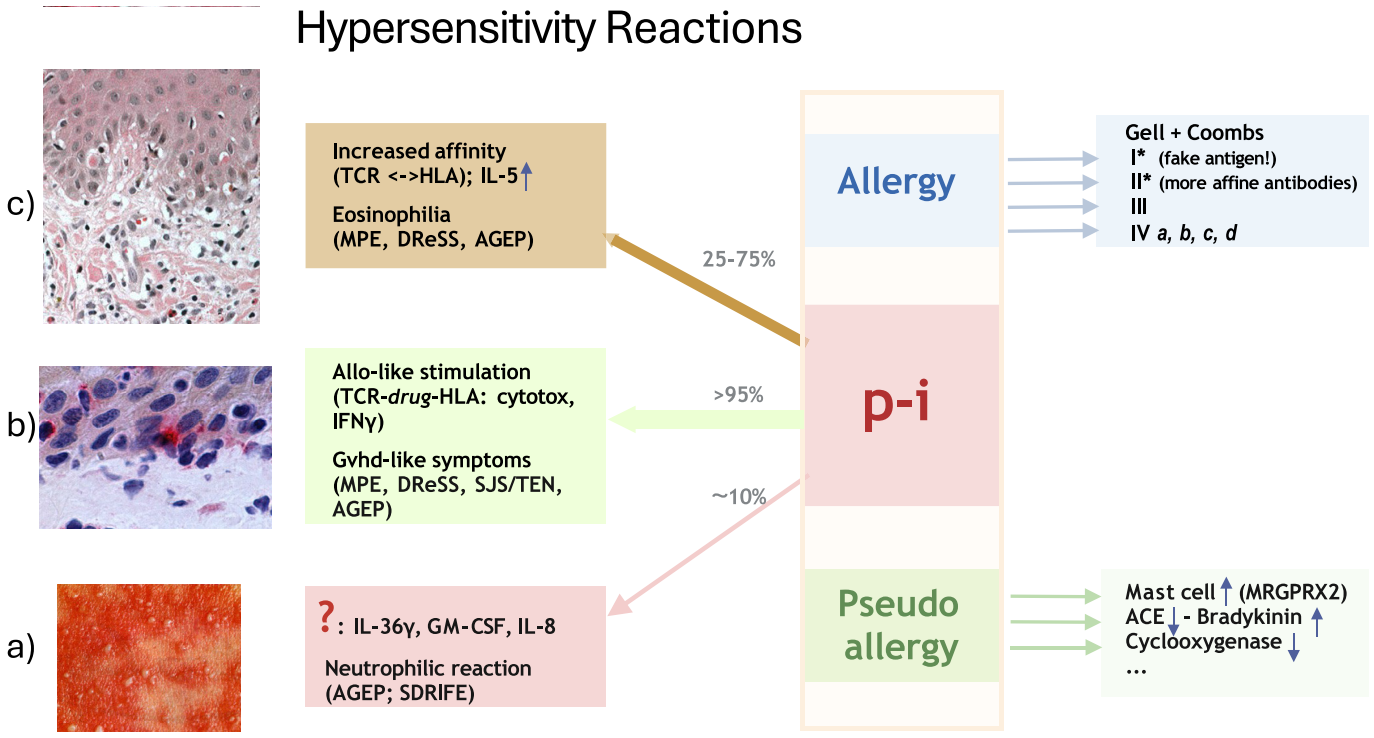

Fig. 4. Classification of drug hypersensitivity: DHRs can be divided into classical antigen driven immune/allergic reactions, p-i, or pseudo-allergic reactions.[1] Classic antigen driven immune/allergic reactions are normally classified according to G&C. They are initiated by formation of a new antigen based on covalent hapten-protein interactions[6,64]: this is important for initiating an antibody response (IgE, IgG) and for Type IV reactions causing contact dermatitis. Classical Type IV may also occur in some MPE due to β-lactams (haptens). But generally, the role of antigen formation as driver of immune reactions appears to be relatively low in systemic dDHR; Note that in type I and II reactions, the effector mechanism may often be elicited by drugs binding *non-covalently* to proteins[5]: *In the context of drug specific IgE reactions, forming a "*fake antigen*" (non-covalent drug–protein binding) may be sufficient to trigger mast cell degranulation and potentially result in anaphylaxis.[76] *In G&C Type II reactions (anemia or thrombocytopenia due to antibodies directed against cell surface determinants), blood cell dyscrasia may occur through the non-covalent association of the drug with anti-blood cell antibodies, which increases their *affinity* towards the cell surface structures of blood cells.[5]
P-i reactions cause direct T-cell activations;
- Cytotoxic/IFNγ-secreting stimulations (p-i cytotox; >95 of dDHR) due to an allo-like stimulation.
- Enhance affinity of TCR↔HLA interaction; this can result in eosinophilia[8] ("p-i IL-5″), or oligoclonal expansion of T cells, observed in SJS/TEN.[19,20,50].
- The development of neutrophilic inflammation due to IL-8, GM-CSF, and IL-36γ seems to occur by a not yet clarified mechanisms.
The clinical consequences of p-i cytotox and p-i IL5 are illustrated by histology: infiltration of perforin+ and CD4+ T cells, hydropic degeneration of keratinocytes, and the presence of eosinophils (b, c). A neutrophilic inflammation of the skin (AGEP) is shown in a). Pseudo-allergic reactions are due to the activation of inflammatory cells (mast cells, basophils, neutrophils, eosinophils) or interference with proteins/enzyme activities, somehow enhancing inflammation (e.g., bradykinin ↑).[1] Specific immunity is *not* involved. As the symptoms imitate IgE-mediated allergic reactions (urticaria, swelling/angioedema, bronchospasm), they are called "pseudo-allergic" reactions.

Some dDHRs, such as AGEP and symmetrical drug-related intertriginous and flexural exanthema (SDRIFE), are characterized by neutrophilic inflammation.[60,61] In some cases of AGEP and SDRIFE, T cell-mediated cytokine secretion and exceptionally high IL-8 and GM-CSF levels have been observed,[62] as well as release of IL-36γ by monocytes/macrophages and keratinocytes.[63] The details of T cell activation and its connection to neutrophil recruitment and activation in DHR remain unclear.

Conclusion and clinical impact: P-i-induced inflammation is distinct from antigen-driven inflammation. MPE/DReSS are not T2-based inflammations, and p-i stimulations/dDHR should not be classified according to the G&C classification[64] but separately as p-i (Fig. 4).

Consequences of chronic manifestations of p-i: viral reactivations, autoimmunity, multiple drug hypersensitivity

Surprisingly, patients with DReSS have circulating activated T cells that persist for years after an acute event.[65] These may continue to be activated even when the drug is avoided due to continuous encounters with cross-reactive peptide antigens and may explain the high precursor frequency observed.[66] These activated T-cell phenotypes (high expression of CD69 and PD1) were similar to those found in chronic gvhd, further highlighting the similarity between allostimulation/gvhd and p-i-induced dDHR (chronic gvhd,[67]).

P-i stimulation may also explain late-appearing *viral reactivation and autoimmunity*.[5,12] Stimulating T cells with p-i can lead to cell expansion and robust immune response.[36] The expanded T cells react with the drug (via p-i), but their TCR may also cross-react with certain immunogenic peptides and their cytotoxicity can cause autoimmune reactions when targeted towards cells presenting self-peptides.[5,12,22]

One of immune system's primary function includes controlling endogenous virus infections, with up to 10% of circulating CD8 T cells in the elderly being specific for herpes virus antigens.[68] The viremia weeks after acute DReSS is generally explained by increased viral replication.[22] Alternatively, p-i may stimulate circulating T cells; when they encounter their specific (viral) antigens in the periphery, their cytotoxic activity is stimulated.[5,12] This could potentially lead to the discharge of viruses and viremia from the infected tissue cells, without enhanced replication.

Multiple-drug hypersensitivity (MDH) can occur due to p-i stimulation in severe dDHR.[69] Approximately 25% of patients with DReSS or severe MPE develop another DHR for chemically distinct drugs. In vitro analysis suggests that T cells with an activated

phenotype are responsible for the response to a new drug.[65] MDH can occur during acute DHRs, such as combination therapy (e.g. cotrimoxazole), shortly after the acute initial phase (week 3–10), or in remission years after the first DHR. The second or third DHR can vary in severity and may involve other organs (such as the bone marrow or heart). Such patients present a therapeutic dilemma, as any new drug may elicit new and dangerous DHRs. Medications with high efficacy at low molar concentrations[69,70] are recommended to minimize off-target interactions with immune receptors (p-i).

Conclusion and clinical impact: p-i stimulation may have long-lasting consequences, resulting in autoimmune diseases, higher viral loads, and the emergence of MDH.

DHRs are not allergies

The primary cause of dDHR (MPE, DReSS, SJS/TEN, AGEP) is drug binding to a subset of vast and highly heterogeneous immune receptors (millions of different TCRs/individual, >40.000 different HLA molecules in the population). This p-i mechanism explains the rarity of the event, as the receptor structure to which the drug might bind with sufficient affinity may only be present in a few individuals. Drug-induced immunology is unorthodox, as it relies on the formation of allo-like, stimulatory TCR-HLA complexes and/or more affine TCR–HLA complexes.

A main result of investigating dDHR over the last 25 years can be summarized as: dDHR is not an allergic reaction. Drug-induced T-cell stimulation in dDHR is drug-driven (p-i) but is not drug-specific (=not directed against the drug acting as antigen). This contrasts with previous beliefs and guidelines for risk management of new drugs. The risk of drug-induced systemic dDHR does not originate from its ability to stimulate classical immune reactions by forming antigens based on covalent bonds with proteins, but rather from alternative stimulation, which occurs due to non-covalent drug binding to immune receptors such as TCR or HLA (5, 71; Fig. 4). Table 3 summarizes the clinical and immunological features of p-i-mediated dDHR and compares them with allo-stimulation (gvhd).

Conclusion and clinical impact: The p-i effect (= transformation of pharmacology to immunology) is linked to an allo-like stimulation (Fig. 2, Table 3). Like in allo-reactivity, there is no prior sensitization. P-i causes expansion of naïve and memory T cells which are able to react directly to the drug altered TCR/HLA[43,72]: the speed of reactivity and appearance of symptoms depends on the amount of structural changes induced by drug binding to HLA/TCR, whereby some drugs bind simultaneously to different sites of the TCR and/or HLA. This contributes to functional and well known clinical heterogeneity of dDHR. After an acute p-i/dDHR, re-exposure may not cause symptoms if the conditions for drug reactivity have changed (e.g. virus co-stimulation, Fig. 1). On the other hand, in severe dDHR the p-i mediated T cell reactivity can persist for years.[5,66] It may be connected to the spectrum of inherent allo-reactivity of the individual. A persisting T cell reactivity can often be demonstrated by skin and in vitro tests in patients with prior MPE and DReSS, but is more difficult in SJS/TEN.[23]

Relevance of p-i

P-i beyond DHR: The relevance of the role of p-i extends beyond DHRs. It may be linked to professional diseases elicited by small chemicals, where p-i could play a role.[73] Drug interactions with the TCR/HLA complex may help decipher the still enigmatic signaling of the TCR/CD3 complex.[41,42] The allosteric effect of sulfamethoxazole on TCR has been previously described.[18] Allosterism has also been discussed as a possible mode of signal transduction in regular TCR-HLA/peptide interactions.[41]

P-i Stimulation – a misunderstanding: dDHR is an artificial iatrogenic disease. A synthetic, newly synthesized chemical initiates p-i stimulation, although the immune system typically ignores these small molecules. However, some substances, particularly if administered at high concentrations, which are actually a main risk factor for dDHR,[1,69] may escape this silent elimination and bind to one of the most critical spots of the specific immune system, namely the HLA-TCR junction. The modification of structural parts

Table 3
Differences of allo-stimulations/gvhd vs. allo-like immune stimulations (p-i) in dDHR.

	Direct Allostimulation/gvhd	dDHR (p-i)
Duration of changes	Permanent (as long as transplant is present)	Transient: the longer the therapy, the more severe reactions (DReSS, SJS: mostly >10 d therapy);
Type of differences	Allo-HLA structure (direct allostimulation); processed HLA (indirect allostimulation → chronic gvhd)	Changes affect HLA or TCR structures directly; no processed neoantigen, as drug–protein binding is too labile to form neoantigen
Duration of "allo-antigen" exposure	permanent after transplantation	As long as drug therapy lasts (2 d – >50 d)
Duration of immune reactions	immunological changes start immediately, become chronic and are perpetuated by indirect allostimulation; crossreactivity; autoimmunity;	An immunological reactivity is initially suppressed; in some cases p-i stimulations and dDHR symptoms develop: enhanced by increased dose, viral co-infections, etc. Acute dDHR symptoms disappear slowly after stop of incriminated drug, as the symptoms are linked to T cell stimulation. T cells can be reactivated in absence of drug due to cross-reactivity with viral- or auto-antigens
Chronic T cell activation	↑ expression of CD69, PD1	↑ expression of CD69, PD1
Virus reactivations	HHV6>EBV/HHV7>CMV	HHV6>EBV/HHV7>CMV
Immunology	Direct (DC independent, memory and naïve T cells, polyspecificity) & long-lasting activation with extensive cross-reactivity (self and viral peptides); Indirect allostimulation (DC dependent, peptide-specific) → chronic gvhd	Direct (DC independent, memory and naïve T cells, polyspecificity) & long-lasting immune activation with extensive cross-reactivity (self and viral peptide), Development of MDH
Clinic	MPE, SJS/TEN, DILI, vasculitis etc. Damage to many organs in chronic gvhd	MPE, DReSS, SJS/TEN, AGEP, DILI
Eosinophilia	Frequent, but not obligatory	Frequent, but not obligatory
Differences	*Permanent* presence of allo-HLA; chronic gvhd with ongoing immune stimulations due to processed alloantigens; continued (strong) immune-suppressive therapy	*Transient* drug therapy and only transient allo-like stimulation; mostly less severe symptoms compared to gvhd due to labile binding and rapid elimination of drug; limited immune-suppressive therapy; Cave re-exposure to the drug in severe reactions;

of the TCR and/or HLA by the drug causes a “misunderstanding”: the involved TCR/T cell gets a signal by the modified {TCR-drug-HLA} complex as if it had encountered an allo-HLA complex. The consequence of this direct alloreactivity can be a full T cell activation (without need of additional co-stimulation![10,43]) and manifests as cytotoxicity, cytokine release, and proliferation of the involved T cells, all of which are triggered by a harmless drug localized at a particular spot.

P-i reveals the immune system's limitation to handling small molecules: that a phenomenon like p-i can happen in our strongly regulated immune system can be interpreted as a sign of overload/overuse of our immune system's capability and capacity. The evolution of the specific immune system occurred in the absence of modern chemistry; the enormous amount of such new chemicals/drugs produced by industries and the substantial doses given in some drug therapies (gram amounts/d) makes it likely that some drugs bind to some of the unique receptor structures in such a way that p-i stimulation is evoked.

P-i in immunology in general:

- P-i has an impact on evaluating the risk of drugs causing dDHR, which means avoiding DHR.[71]
- While p-i/dDHR is often considered an elicitor of adverse side effect, this view may be biased. The activation of T-cells by p-i is likely an extraordinary and rare event, similar to many puzzle pieces coming together to form a complete picture (→stimulatory immune response). This presents an exceptional opportunity to learn about the diverse forms of TCR signaling and allo-like reactivity, two still enigmatic issues in immunology.
- P-i reveals alternative and highly effective methods of stimulating T cells through drug-induced mechanisms, potentially opening up a new type of pharmaco-immunology. Controlling p-i immune reactions through drugs targeting the TCR/HLA complex, the opportunities seem endless. The observation that different manifestations of DReSS (hepatitis, nephritis, etc.) differ according to the type of drug[74] or HLA background supports this idea.[58,75] For instance, carbamazepine and HLA-A*31:01 manifests as DReSS, *15:02 usually as SJS.[75]

P-i needs to be put on a broader basis: the p-i concept offers a radically different view of DH than the previous hapten concept (Fig. 4). There are many open questions, and it is evident that the data warrant a more extensive context, confirmation and that additional p-i-stimulating substances must be investigated, as each drug may possess a distinct mechanism of action.

In spite of these limitations, this review is hopefully able to draw attention to dDHR and to show that these peculiar, iatrogenic diseases are a model for unorthodox immune stimulations, which link pharmacology with immunology. A better understanding of p-i may not only help to prevent or avoid dDHR, but may provide valuable insights into T-cell signaling and may even offer a new way of specific immune stimulation triggered by a drug.

Conflict of interest

WJP is employed by ADR-AC GmbH; Consulting for “Innomedica” in 2022/23.

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