Pathomechanism of Severe Drug Allergy

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Severe drug allergy

- **Type I, IgE**: Anaphylaxis
- **Type II, Ab & FcR**: Blood cell dyscrasia
- **Type III, immunocomplexes, Fc & C`**: Vasculitis
- **Type IV T cells**: T cell orchestrated inflammations, all organs
Delayed T-cell mediated drug hypersensitivity

- Maculopapular exanthema
- acute generalized exanthematous pustulosis (AGEP)
- Stevens-Johnson Syndrome (SJS), toxic-epidermal necrolysis (TEN)
- interstitial pneumonitis
- interstitial nephritis
- Hepatitis
- DRESS
6 yr old girl, epilepsy (Carbamazepin for 3 weeks)
60 yr old man with fatal DRESS (fulminant hepatitis, liver transplantation, death)

CD3+ (mostly CD8+) T-cells
Severe systemic reactions

DRESS

DRESS and haematophagocytic syndrome

Toxic epidermal necrolysis

~ 10% lethality

34% lethality
Late Reaction

Very few precursor cells

After a certain amount of T-cells is reached, symptoms of drug hypersensitivity develop
Late reactions

When does it start?

• 1-3d (if very, very strong sensitization)

• 8-10d (in maculopapular reactions)

• 14->56d (in SJS, DRESS, hepatitis, ....)
Drug hypersensitivity - patho-physiology -

Two questions

• How can one explain the heterogeneity of drug allergic diseases?

• How are T cells stimulated by drugs?

(T cells were found to be crucial)
Drug specific T-cell clones (TCC) from blood and tissue

Cell culture with drug

Expansion of a single cell

Phenotype function: cytokines, cytotoxicity interaction with APCs, tissue cells drug recognition cross-reactivity TCR structure

Perforin - CD4 red - brown

In vitro

Ex vivo
T-cells react with the drug and exert, dependent on their function, a certain pathology.
T-cells react with the drug and exert, dependent on their function, a certain pathology.

- **Amoxicillin**
  - bullous E.
  - cytotoxicity (CD8+)
    - IFN\(\gamma\); IL-5
  - MPE
    - cytotoxicity (CD4+)
      - IL-5; IFN\(\gamma\)
  - AGEP
    - cytotoxicity
      - IL-8; IL-5
### Delayed hypersensitivity reactions type IV a, IV b, IV c, IV d

<table>
<thead>
<tr>
<th></th>
<th>Type IV a</th>
<th>Type IV b</th>
<th>Type IV c</th>
<th>Type IV d</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Immune reactant</strong></td>
<td>IFNγ, TNFα (T&lt;sub&gt;H&lt;/sub&gt;1 cells)</td>
<td>IL-5, IL-4/IL-13 (T&lt;sub&gt;H&lt;/sub&gt;2 cells)</td>
<td>Perforin/ GranzymeB (CTL)</td>
<td>CXCL-8. GM-CSF (T-cells)</td>
</tr>
<tr>
<td><strong>Antigen</strong></td>
<td>Processed antigen or direct T cell stimulation</td>
<td>Processed antigen or direct T cell stimulation</td>
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</tr>
<tr>
<td><strong>Effector</strong></td>
<td>Macrophage</td>
<td>Eosinophils</td>
<td>T cells</td>
<td>PMN</td>
</tr>
<tr>
<td><strong>Example of hypersensitivity reaction</strong></td>
<td>Tuberculin reaction, Contact dermatitis, maculo-papular exanthema with eosinophilia, atopic dermatitis chronic asthma, chronic allergic rhinitis</td>
<td>Contact dermatitis Maculopapular and bullous exanthema, AGEP</td>
<td>AGEP; Behçet disease</td>
<td></td>
</tr>
</tbody>
</table>
Antibody mediated hypersensitivity reactions (I-III) and delayed type hypersensitivity reactions (IV a-d)

<table>
<thead>
<tr>
<th>Immune reactant</th>
<th>Type I</th>
<th>Type II</th>
<th>Type III</th>
<th>Type IV a</th>
<th>Type IV b</th>
<th>Type IV c</th>
<th>Type IV d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Igg</td>
<td>IgE</td>
<td>IgG</td>
<td>IgG</td>
<td>IIFNγ, TNFα (TH1 cells)</td>
<td>IL-5, IL-4/IL-13 (TH2 cells)</td>
<td>Perforin/GranzymeB (CTL)</td>
<td>CXCL-8, GM-CSF (T-cells)</td>
</tr>
<tr>
<td>Antigen</td>
<td>Soluble antigen</td>
<td>Cell- or matrix-associated antigen</td>
<td>Soluble antigen</td>
<td>Antigen presented by cells or direct T cell stimulation</td>
<td>Antigen presented by cells or direct T cell stimulation</td>
<td>Cell-associated antigen or direct T cell stimulation</td>
<td>Soluble antigen presented by cells or direct T cell stimulation</td>
</tr>
<tr>
<td>Effector</td>
<td>Mast-cell activation</td>
<td>FcR+ cells (phagocytes, NK cells)</td>
<td>FcR+ cells</td>
<td>Complement</td>
<td>Macrophage activation</td>
<td>Eosinophils</td>
<td>T cells</td>
</tr>
</tbody>
</table>

Example of hypersensitivity reaction

| Allergic rhinitis, asthma, systemic anaphylaxis | Some drug allergies (e.g., penicillin) thrombocytopenia | Serum sickness, Arthus reaction | Tuberculin reaction, contact dermatitis (with IVc) | Chronic asthma, chronic allergic rhinitis | Maculopapular exanthema with eosinophilia | Contact dermatitis | Maculopapular and bullous exanthema hepatitis | AGEP Behçet disease |

Immune reactant: IgE (Type I), IgG (Type II), IgG (Type III), IIFNγ, TNFα (TH1 cells) (Type IV a), IL-5, IL-4/IL-13 (TH2 cells) (Type IV b), Perforin/GranzymeB (CTL) (Type IV c), CXCL-8, GM-CSF (T-cells) (Type IV d)
How are T cells stimulated by drugs?

The \textit{p-i} concept

\textit{p}harmacological interaction with \textit{i}mmune receptors

The \textit{hapten} concept
Hapten/prohapten specific immunity

Haptens are chemically reactive compounds able to bind covalently to proteins.

Adduct formation gives a danger signal to APC (CD86 upregulation, IL-1β–secretion)

Adduct formation forms neoantigenic determinants able to induce both a T-cell and B-cell immune response. A hapten stimulates both T-cells and B-cells!!
The *p-i* concept

*Pharmacological Interaction with Immune Receptors*

A chemically inert drug, unable to covalently bind to proteins, „happens“ to bind (via hydrogen bonds, electrostatic interactions,...) to some of the many immune receptors (as it does to other proteins/receptors). This drug-receptor interaction can occur with TCR (10x10^{11}/individual) or to certain HLA molecules (>7400/population).
p-i concept
(pharmacological interaction with immune receptors)

Antigenic hapten-carrier complexes induces T cell responses

Drugs bind directly…
B) to the TCR
C) to the MHC
p-i concept:

a) the drug binds to the TCR (by non covalent bonds; not restricted to a HLA-allele)

or

b) the drug binds to the HLA molecule, and the HLA-peptide-drug complex is then recognized by the TCR (HLA-class I restricted, CD8)
p-i concept: a drug fits into a particular HLA molecule

the drug binds to an allele-typic region in the HLA; van der Waals forces; the HLA-peptide-drug complex is then recognized by the TCR

HLA-B*5701: binding groove at position Y116, N114
Only a particular HLA-allele allows binding of the drug in a way, which results in immune stimulation; The relevant allele may be common (~ 1 / 20) or rare (< 1 / 2000) in the population (e.g. 15% of Han chinese carry B*1502 but <0.1% of caucasians)
HLA polymorphism in population
ca 14 HLA allele / individual
> 7400 HLA alleles in human population
some allele the same, some are different

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HLA
- A*02:01, A* 51:01
- B*10:02; B*57:01
- C* 02:01; C*06:01
- DR* B1 01:01; 04:02
- DR* B5 01:01
- DP* 04:04; 08:01
- DQ* 01:05; 05:01

Mister Lee

HLA
- A*02:01, A* 56:01
- B* 15:02; B*58:01
- C* 0201; C*06:01
- DR* B1-01:01; 04:02
- DR* B5-01:01
- DP* 03:04; 07:01
- DQ* 02:04; 03:02
HLA polymorphism in population
ca. 14 HLA alleles / individual
ca. 7800 HLA alleles in human population
some allele are frequent, some are rare

Mister Meyer

- A*02:01, A* 51:01
- B*10:02; B*57:01
- C* 02:01; C*06:01
- DR* B1 01:01; 04:02
- DR* B5 01:01
- DP* 04:04; 08:01
- DQ* 01:05; 05:01

Risk for
Abacavir
hypersensitivity

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- A*02:01, A* 56:01
- B* 15:02; B*58:01
- C* 0201; C*06:01
- DR* B1-01:01; 04:02
- DR* B5-01:01
- DP* 03:04; 07:01
- DQ* 02:04; 03:02

Risk for
Allopurinol
Hypersensitivity

Risk for
Carbamazepine
hypersensitivity
The p-i concept

Pharmacological Interaction with Immune Receptors II

The drug interaction with HLA molecules is often involving certain HLA-alleles – which explains the HLA association of some drug hypersensitivity reactions (abacavir, carbamazepine, allopurinol, flucloxacillin,...).

• The drug binding may alter the HLA-peptide complex or exchange the peptide presented: this stimulates an auto(peptide) or allogeneic immune response.

  or

• The drug binds to the variable region of the TCR. This enhances the interaction of TCR with certain peptide - HLA complexes and elicits reactions similar to superantigen stimulations.
Drug binding to HLA: **Altered self peptide repertoire** or **changed HLA-peptide shape**

**w/o abc**

**with abc**

Adapted from Ostrov et al., Proc Natl Acad Sci. 2012 May 29
Drug binding to HLA: altered self peptide repertoire or changed HLA-peptide shape (alloreactivity)

with abc

T cell

HLA

APC

alloreactivity
p-i concept:

- The drug binds to the TCR (by non-covalent bonds; HLA-allele not restricted).

The drug binds to the HLA molecule, and the HLA-peptide-drug complex is then recognized by the TCR (HLA-class I restricted, CD8).
SMX-specific Clone 1.3:
SMX binds to the beta loop of CDR3 (TCR)
p-i concept: some clinical mysteries are solved

- clinical manifestations of DH and skin tests to inert compounds
- rapid appearance without prior sensitization
- uncontrolled (superantigen like) reactions (SJS/TEN, DRESS)
- HLA associations
- gvhd like clinical features
- drug induced autoimmunity
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• Are (delayed) skin tests positive in p-i stimulations?
  Yes, sometimes they are only positive in p-i stimulations, as the metabolism required for hapten formations is absent in the skin but the reactive cells are present

• Are p-i stimulations „sensitizations“ (= complex immune responses)?
  not really, but they can cause expansions of T cells reacting with the drug, which later fulfill effector functions

• Are drug reactive T cells „specific“ for the drug and do they undergo selection in the thymus?
  No, the drug reactive cells are not „specific“ for the drug, but are actually specific for a peptide antigen (and selected for peptide reactivity in the thymus); they often show some alloreactivity
• Are p-i stimulated T-cells persisting (memory)?
  Yes, the reactive T cells seem to persist for many years.
• Which stimulations are more frequent, (pro-)hapten or p-i:
  in contact dermatitis probably hapten, in generalized drug reactions probably p-i.
• Are p-i stimulations relevant for severe drug reactions:
  yes, cytotoxic T cells from blister fluids of SJS/TEN patient were p-i reactive. P-i clones were also seen in DRESS/DiHS, AGEP, MPE, contact dermatitis.
• Are p-i reactive T cells cytotoxic, or IFNγ producing or IL-5 producing...
  yes, the function is as broad as the one of hapten stimulated T cells. It is as variable as the peptide specific T cell immune response.