Genetic in Severe Drug Allergy Reactions

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Severe Drug Hypersensitivity Reaction

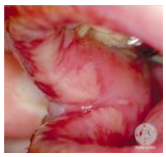
DRESS *Drug Rash with Eosinophilia and Systemic Symptoms*

- Other Names: DHS, DIHS
- Fever
- Massive eosinophilia (> 1,5G/Lt), lymphoadenopathy)
- Internal organ: liver, kidney, lungs
- Late onset of the symptoms (> 2-10 Weeks treatment)

Severe Drug Hypersensitivity Reaction

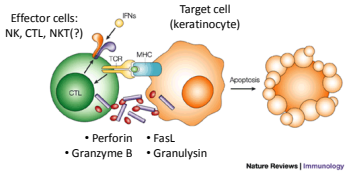
SJS / TEN

- Stevens Johnson Syndrome (SJS, 10 % Body surface)
- Toxic Epidermo Necrolysis (TEN, > 30 % Body surface)
- Caused by drug hypersensitivity >95%
- Mortality: - 10-35%
- Massive keratinocyte apoptosis
  - Epidermal detachment / Formation of bullea
- Involvement of mucosae



Pathogenesis Present Concept

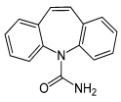
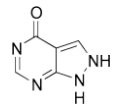
- Immune mediated
  - Adaptive immunity
  - Activation and clonal expansion of T cells
  - MHC-restricted drug presentation → HLA Class I association
  - Initiation by cytotoxic T lymphocytes (CTL)
- Immune mediated Cytotoxicity:



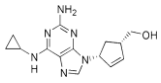
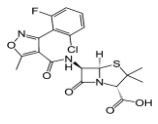
Genome wide association studies

- Rapid scanning of markers across the genome of many people to find *genetic variations* associated with a particular disease.
- Patients cohorts
  - Patients with SJS/TEN or DRESS due to a define drug
  - Patients tolerating the drug
  - Healthy individuals (not exposed to the drug)

Genetic association with DHR

Carbamazepin 	- **HLA-B*1502** in Han-chinese 100 % association (SJS) 3% positive predictive value - **HLA-A*3101** in Japanese population 60.7% association (SJS) OR 10.8 - **HLA-A*3101** in european population OR 12.4 (DRESS) 8.6 (MPE), 25.9 (SJS)	Chung et al., Nature 2004 Ozeki et al., Hum Mol Genet 2011 Mc Cormack et al. NEJM 2011
Allopurinol 	- **HLA-B*5801** in Han-chinese 100% association (SJS & TEN) - **HLA-B*5801** in Caucasian 55% association (SJS) OR 80 Undefined association for allopurinol-induced DRESS	Hung et al., PNAS 2005 Lonjou et al. Phamacogen. 2008

Genetic association with DHR (2)

Abacavir 	**-HLA-B*5701** 100% association of confirmed cases 55% positive predictive value Symptoms similar to DRESS *Personalized medicine* (typing required)	Mallal et al. NEJM 2002
Flucloxacillin 	**-HLA-B*5701** Drug induced liver disease (DILI) 84.3% association in a DILI-cohort OR 80 Prevalence: 1 in 500-1000 HLA-B*5701+	Daly et al. Nature Gen 2009

Genetic associations and functional involvement

Absolute **100%** association:

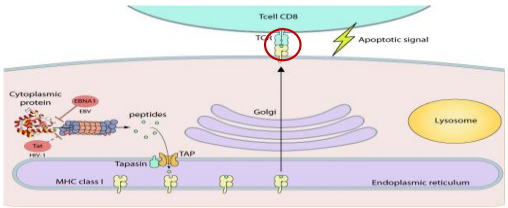
Carbamazepine	HLA-B*1502: **100%** (Han Chinese)
	HLA-A-*3101: **>60%** (Caucasian)
Allopurinol	HLA-B*5801 **100%** (Han Chinese)
	HLA-B*5801 **>50%** (Caucasian)
Abacavir:	HLA-B*5701 **100%**

Seeing these extremely high proportions of identified HLA allele in cohorts, **HLA molecules must be functionnally involved** in the pathogenesis of drug hypersensitivity desorders!

What are HLA molecules?

Membrane surface proteins presenting peptide antigens to T cells:

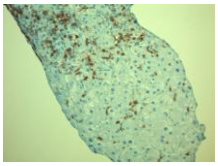
- MHC class I, HLA-A, - B and - C → CD8+ T cells
- MHC class II, HLA-DP,-DQ, DR → CD4+ T cells



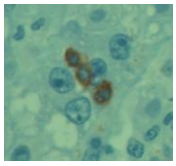
Viralzone Expasy

Involvement of T cells in severe hypersensitivity reaction

- HLA associations prefernatially with HLA class I
- CD8 activation
- Cytotoxic mechanism (Granzyme B, Granulysin)
- Severe reactions (SJS, hepatitis)



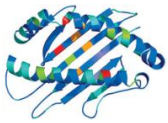
CD 8 Staining



Perforin staining

Top view of the HLA-molecule

Empty HLA molecule

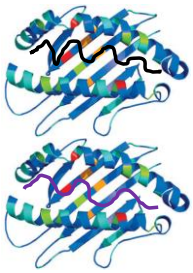


Bharadwaj et al. JACI 2011

Extremely polymorphic

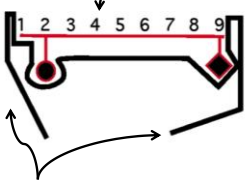
➢1500 alleles identified

Peptide containing HLA molecules



Side view of the HLA-molecule

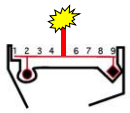
Anchored peptide : multitudes of possible peptides



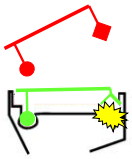
HLA molecule

Positions 2 and 9 are called "*anchor residues*" because they fix the presented peptide by tight interaction with the HLA molecule

Possible mechanisms involving HLA association

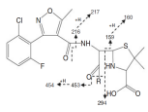


Hapten theory

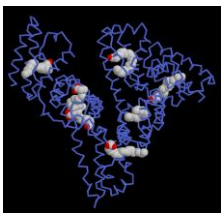


Interaction within the Peptide binding groove

Hapten mechanism

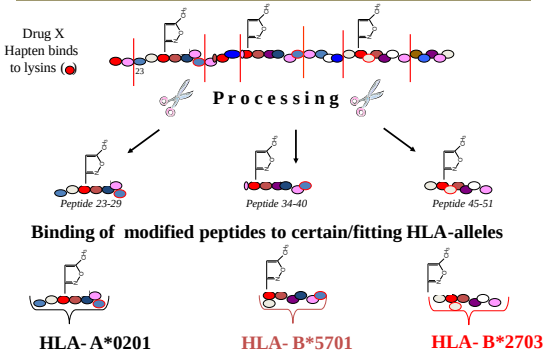


Jenkins et al., 2009 Proteomics



Covalent binding of the drug on proteins

How could be the presentation of haptenized peptides HLA allele restricted



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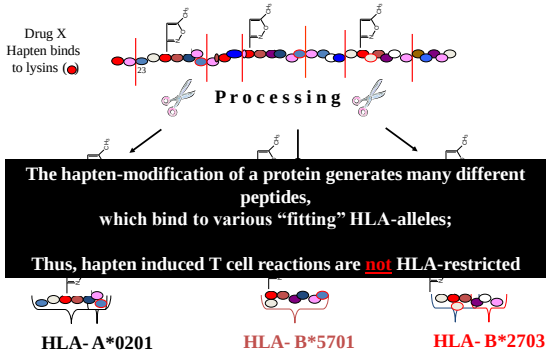
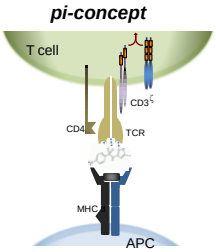
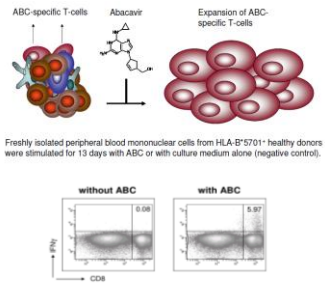


pi-concept: Pharmacological Interaction with Immune Receptors



Labile, non-covalent interaction

The Abacavir model



Small polymorphism between within the B*57/58 haplotype

B*5701 B*5702 B*5801

114 Asp → Asn
116 Ser → Tyr
156 Leu → Arg

45 Met → Thr
46 Ala → Glu
97 Val → Arg
103 Val → Leu

Small polymorphism between within the B*57/58 haplotype

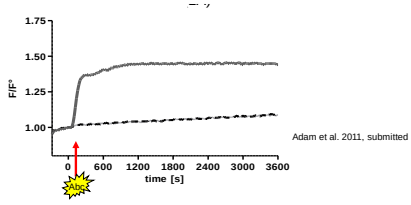
B*5701 B*5702 B*5801

114 Asp → Asn
116 Ser → Tyr
156 Leu → Arg

45 Met → Thr
46 Ala → Glu
97 Val → Arg
103 Val → Leu

Immediate activation of specific CD8+ T cells by Abacavir

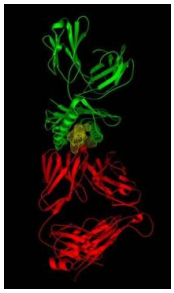
Intracellular Calcium influx measurement



→ 200 seconds are to short to allow processing of Abacavir modified peptide

Carbamazepin model: Absence of modified peptides

HLA-B*1502 eluted peptide did NOT carry the drug (CBZ).
Yang CW, JACI, 2007

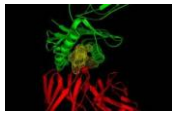


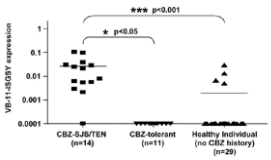
Why Carbamazepine induces SJS/DRESS in less than 5% of HLA-B*1502+ individuals?

HLA-B*1502

- 100% association in the cohort
- But <5% of HLA-B*1502 will develop SJS to CBZ
- Specific Clonotype in the population

Ko et al, *JACI, 2011*





Summary

- GWAS identified HLA-allele association with severe drug hypersensitivity
  - Carbamazepin: HLA-B*1502/A*3101
  - Allopurinol: HLA-B*5801
  - Abacavir, Flucloxacillin HLA-B*5701
- Genetic associations were discovered with very high proportions (100%!) in DHR cohorts.
- Abacavir and HLA-B*5701 typing: first example of successful personalized medicine

Summary (2)

- HLA molecules are crucial protein involved in peptide antigen presentation
- Drug can interact with HLA at very precise locations and produces / modifies antigenic determinants
- Phenotype of main in-vitro generated drug reacting T cells is inflammatory (IFNγ production) and cytotoxic.

Aknowledgements

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