Cellular and Molecular Mechanisms of Allergic Diseases

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Two types of allergic diseases-I

monoallergy (allergic breakthrough)

high specific IgE without atopy

high success of allergen-SIT

in most cases no typical organ involvement venom allergy
Insect venom allergy
The first recorded death from an insect allergy was King Menes of Egypt, who, according to the hieroglyphics on his tomb, died of a wasp sting in 2621 B.C.
Two types of allergic diseases -II

polyallergic and inflammatory
atopic diseases (true atopy)

dermatitis, asthma, rhinitis

high total IgE,
high specific IgE to many allergens,
eosinophilia
A typical family history of atopy

Emperor Augustus: suffered from bronchial asthma, seasonal rhinitis and atopic eczema

Emperor Claudius: perennial rhinoconjunctivitis

Britannicus: horse dander allergy
King Richard III (1452-1485) used his allergy to strawberries to arrange the murder of Lord William Hastings.

He ate some strawberries and developed acute urticaria.

He then accused Hastings of putting a curse on him, an action that demanded the head of Hastings on a plate.
atopic dermatitis
asthma
rhinitis
allergic
inflammation
T cell interaction with other cells and effector functions (epithelial apoptosis, hyper IgE eosinophilia)
T cell survival and reactivation in the subepithelial tissue
aeroallergens, food antigens, autoantigens, superantigens, yet unidentified factors induce T cell activation
organ-selective T cell homing under the control of chemokine network
activation
allergic inflammation
effector functions
homing
survival and reactivation
Th1 and Th2 cell balance in disease

Th1

IFN-γ
TNF-α, β

Th2

Allergy

IL-4
IL-5
IL-6
IL-9
IL-13
IL-25
Th1 and Th2 cell balance in homeostasis

IFN-γ, TNF-α, β

IL-4, IL-5, IL-6, IL-9, IL-13, IL-25

Th1

IL-10 / TGF-β

T_{Reg}

Th2
**Major Functions**

- **IL-10 / TGF-β**

**IFN-γ**

**TNF-α, β**

**Th1**

- DTH
- Macrophage activation
- Limited B cell help/inhibition

**Th2**

- B cell help
- Eosinophil mast cell stim.
- Macrophage inhibition

**T_{Reg}**

- Inhibition of Th1 Th2 cells
- Inhibition of mo/mac
- Inhibition of DC maturation
Apoptosis: programmed cell death activation-induced cell death

essential mechanism in homeostasis

In atopic dermatitis and asthma, cells involved in the pathogenesis show different survival and apoptotic properties
Cutaneous lymphocyte-associated antigen-bearing skin homing T cells (CLA+)

- In vivo activated
- Spontaneously proliferating
- Th2-like cytokine profile (IL-5, IL-13)
- Induce IgE (IL-13)
- Prolonge eosinophil life span (IL-5)

Akdis et al. J. Immunology 1997, 1999
Increased death of circulating CLA$^+$ T cells in AD
Histopathology of AD

- 70% T cell
- 1-3% Eosinophil
- 10-20% Dendritic cell
- CD4/CD8 ratio: 2

Pathological features:
- Eczema/spongiosis
- Effector functions
- Survival/reactivation
- Activation/homing

Pathological components:
- Dermal mononuclear cells
Skin T cells do not die although they express both Fas and Fas-ligand in AD
Skin T cells do not die although they express both Fas and Fas-ligand in AD

Akdis et al. Faseb J 2003
Early 0-2 days
Th2/Th0-like

IL-4
IL-5, IL-13
IFN-γ

Late 3-6 days
Th0/Th1-like

IL-12
IFN-γ
IL-5, IL-13
IL-4
resting T cells

activated T cells

no apoptosis

apoptosis

IFN-γ
Fas-ligand
TNF-α

cocultures

resting T cells

activated T cells

IFN-γ
Fas-ligand
TNF-α

artificial skins
Activation and apoptosis of epithelial cells induced by subepithelial inflammation

Key pathogenetic event in atopic dermatitis and asthma

counter signals from the epithelial cells augment inflammation

J Immunol 1997
J Immunol 1999
EJI 2000
J Clin Invest 2000
Curr Opin Imm 2000
Trends Immunol 2001
J Allergy Clin Immunol 2001
J Invest Derm 2001
J Allergy Clin Immunol 2002
J Allergy Clin Immunol 2003
J Immunol 2003
Faseb J 2003
Curr Opin Immunol 2004
J Allergy Clin Immunol 2005
J Allergy Clin Immunol 2006
Curr Opin Immunol 2006
allergy: intolerance to allergens

autoimmunity: intolerance to autoantigens

transplantation rejection: intolerance to transplanted organ

chronic infection: neutralization defect of infectious agents because of tolerance

cancer: inappropriate immune response to tumor antigens because of tolerance
IL-10-induced peripheral T cell tolerance in bee venom specific-immunotherapy

IL-10 production in T cells during specific immunotherapy

CD4⁺ CD25⁺ T_{reg} cells

day 0
day 7
day 28
IL-10 and TGF-β in peripheral T cell tolerance during aeroallergen SIT

n= 10, SIT cluster protocol, Der p 1-stimulated PBMC

Jutel et al.
**T_{Reg} cells in allergy: a question of balance**

before SIT allergic  

after SIT healthy
IL-10-mediated peripheral T cell tolerance during natural bee stings

a model for natural high dose antigen/allergen exposure

more than 20 bee stings in one week
Antigen-specific peripheral T cell tolerance

[3H]-thymidine incorporation (cpm x 1000)

months of the year

J F M A M Ju Jl A S O N D

bee keeping season
Changes in cytokine profile after bee stings

Changes in cytokine profile after bee stings.

n=6, 5d Ag+7d IL-2 expansion, restimulation anti-CD3/28 4h.
Frequency of PLA-specific cytokine secreting T cells before and after live bee stings

Decreased frequency of PLA-specific IL-4- and IFN-γ-secreting T cells, increased frequency of IL-10-secreting T cells is observed 7 days after ≥20 bee stings.

*: p<0.001
n:5 beekeepers
Aerollergen-specific T cell frequency in health and allergy

**Figure:**

- **Allergic** and **Healthy** samples compared for frequency of T cells expressing IL-4, IFN-γ, and IL-10.

- **Markers:**
  - Red squares: Der p 1
  - Yellow triangles: Bet v 1
  - Blue circles: Pyr c 5
  - White squares: Cor a 1

- **Significance:**
  - *: p < 0.05
  - **: p < 0.01

**Source:** Akdis et al. J Exp Med 2004;199:1567-75
Which one will be the first T cell to contact APC in an ongoing memory response?
T_{Reg} cells in allergy: multiple suppressor factors

<table>
<thead>
<tr>
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<th>IL-10</th>
<th>IL-10R</th>
<th>CTLA-4</th>
<th>CD25</th>
<th>PD-1</th>
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<td>CD4+</td>
<td>75.1</td>
<td>83.3</td>
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<td>IL-10+</td>
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<tr>
<td>CD3+</td>
<td>9.1</td>
<td>0.6</td>
<td>0.6</td>
<td>11.6</td>
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CD4+ IL-10+ T_reg cells in allergy: multiple suppressor factors

IC TGF-βRII TGF-βRI

CD4+ IL-10+
IL-10 suppresses IgE and induces IgG4
TGF-β suppresses IgE and induces IgA
IL-10, TGF-β and their receptors are expressed in AD skin

Verhagen et al. JACI 2006
CD4+CD25+FoxP3+ T\textsubscript{Reg} cell deficiency in atopic dermatitis and psoriasis lesions

Verhagen et al. JACI 2006
$T_{Reg}$ cells in healthy immune response and successful SIT

- Suppression of effector cells
- Allergen-specific $T_{reg}$ cell
- Multiple suppressor factors: IL-10, TGF-$\beta$, IL-10R, TGF-$\beta$R, CTLA-4, PD-1, HR2
- Induction of IgG4, IgA

J Clin Invest 1996
J Clin Invest 1998
FASEB 1999
FASEB 2001
Immunology Today
Immunology 2001
Nature 2001
Eur J Immm 2003
FASEB 2003
Nature Rev Imm 2003
J. Exp. Med 2004
• Axel Trautmann
• Sven Klunker
• Alison Taylor
• Johan Verhagen
• Maya Zimmermann
• Flurina Meiler
• Judith Zumkehr
• Tomasz Basinski

• Reto Crameri
• Carsten Schmidt-Weber
• Cezmi Akdis

**Immune tolerance**

- U. Müller, Bern
- B. Wüthrich, Zurich
- M. Jutel, Wroclaw, SIAF
- R. Valenta, Vienna
- E. Jensen-Jarolim, Vienna
- M. van Hage-Hamsten, Stockholm
- G. Gavfelin, Stockholm
- R. Kroczek, Berlin
- M. Colonna, St Louis
- E. Flory, Langen
- S. Viehts, Langen
- H. Fiebig, Reinbek
- C. Heusser, Basel
- E. Hamelmann, Berlin
- M. Larchè, London
- A. Verhoef, London
- S. Alkan, Minneapolis
- R. Lauener, Zurich
- B. Ballmer-Weber, Zurich

**Mechanisms of atopy**

- R. Disch
- B. Wüthrich
- P. Schmid-Grendelmeier
- W. Kneist
- M. Schliz
- D. Kleeman
- W. Deglmann
- H. Behrendt,
- C. Traidl-Hoffmann, Munich

**Immune regulation by histamine**

- T. Watanabe, Osaka
- R. Koga, Fukuoka
Philosophy of the meeting

As ever, immune regulation is the hottest issue in basic and clinical sciences. No question that we need to gather and get inspired. With an outstanding list of speakers in this field, „Immune Regulation – Davos“ becomes the key event of the year 2007, being big enough to learn from other disciplines and small enough to personally meet the experts.

Davos has been stimulating not only for scientists, but also for other meetings such as the World Economic Forum, held every year in the same conference center. There will be long lunch breaks, allowing to digest attended symposia, to talk with colleagues, while enjoying the winter sports and landscape. The evening sessions will give young researchers the opportunity to meet senior scientists. As at other Davos meetings, we will come together for poster sessions with deserts and drinks providing a relaxed and stimulatory atmosphere for scientific exchange.

Practical workshops

A practical course on flow cytometric and Treg analysis will be performed at the Swiss Institute of Allergy and Asthma Research. This course will provide first-hand expertise on Treg-analysis facilitating your research. The course is planned both for scientific fellows and technical assistants. It will be an ideal complementation for the theoretical background provided by the meeting and will be supported by flowcytometer experts as well as researchers from SIAF. Several other workshops are being planned and details will be announced on our website.

Organisator:
Cezmi Akdis
Organizing comitee:
Carsten Schmidt-Weber
Mübeccel Akdis
Reto Cramer
In:
Davos, congress center
Abstract submission:
Early registration deadline:
15 December 2006
Meeting style:
Symposium & workshop, practical workshops
Meeting organization:
This meeting is organized by the Swiss Institute of Allergy and Asthma Research (SIAF), a non-profit, University associated foundation
SIAF, Obere Str. 22, CH-7270 Davos
Treg meeting.Davos@siaf.unizh.ch
Registration Fee:
500.- Swiss Francs
Fellows in training: 200.- Swiss Francs
Bronchial biopsies

HE

Normal

Asthma

Asthma

Asthma

TUNEL

TNF-α

IFN-γ

Fas-ligand

Trautmann et al. 2002, 2005
IFN-\(\gamma\), Th1, IL-10, T\(_\text{Reg}\), IL-4, Th2, autoimmunity, allergy, immune tolerance
Purification of allergen-specific cytokine-secreting T cells
local IgE production

smooth muscle cell activation and hyperreactivity for contraction, release of chemokines and proinflammatory cytokines

Th2

increased endothelial cell adhesion and transmigration of inflammatory cells

Histamine

increased mucus production

bronchial epithelial cells

lungs

epithelial activation, release of chemokines and proinflammatory cytokines

spongiosis

induction of bronchial epithelial cell and keratinocyte activation and apoptosis

a second step of T cell activation and proliferation by IgE-facilitated and non-facilitated presentation of allergens and superantigens by inflammatory DC

basophil entry to tissues mast cell and basophil degranulation and release of monoamines, lipid mediators, chemokines and proinflammatory cytokines

epithelial activation, release of chemokines and proinflammatory cytokines

increased mucus production

apoptotic epithelial cells

skin