An immunological overview of allergen specific immunotherapy**Subcutaneous &Sublingual routes**

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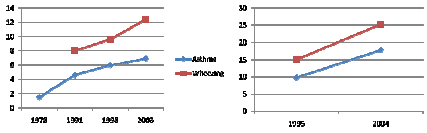
Burden of allergic disorders increase

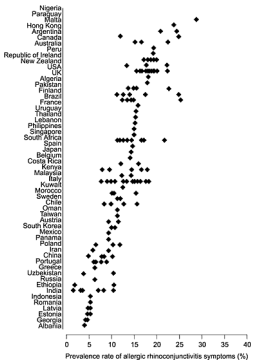
Asthma
Allergic Rhinitis
Atopic Dermatitis
Urticaria &Angioedema
Food, Latex, Drug & Venom Allergy
ANAPHYLAXIS



Greece Turkiye

Anthracopoulos MB et al, Arch Dis Child 2007
Ones U et al, Allergy 2006

- Prevalence
- Changes in life styles
- Awareness
- Developments in diagnostic approaches



ISAAC Steering Committee

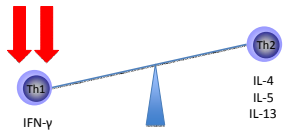
ATOPY

propensity to exert a Th2 response

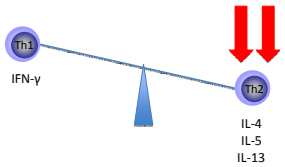
Allergic immune response

- basically an antibody mediated disorder
- characterized by production of allergen-specific IgE and its effects on effector cells.

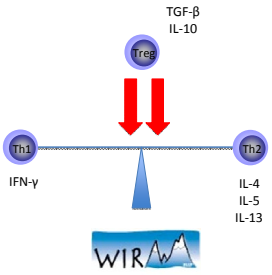
???
an imbalance between Th1 and Th2



autoimmunity meetings



allergy meetings

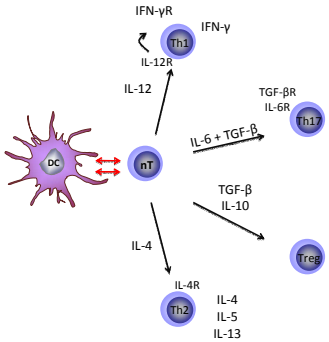


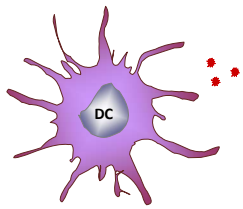
Davos
www.wirm.ch

SIAF

Key players in allergic inflammation

- type of the antigen (allergen)
- presentation to the immune system
- content of the microenvironment
  - cytokines,
  - cellular elements
  - effector cells
  - co-stimulators





capture and engulf

Tolerogenic function

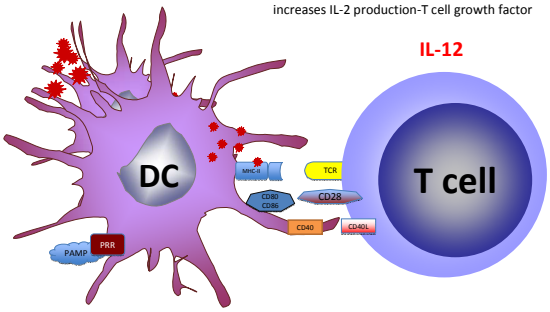
control
Peripheral tolerance & immunity

interact with T and B cells

↓

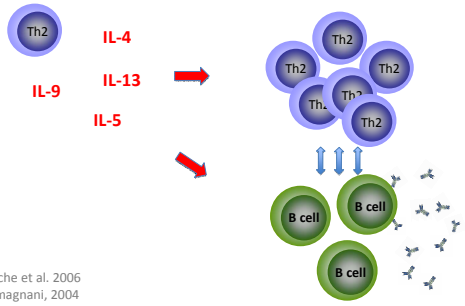
initiate and shape
the **adaptive**
immune response

Costimulatory signaling through CD28 increases IL-2 production-T cell growth factor

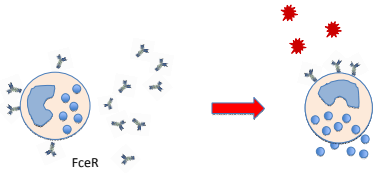


Akdis, 2006
Larche et al. 2006
Romagni et al. 1989

In atopics

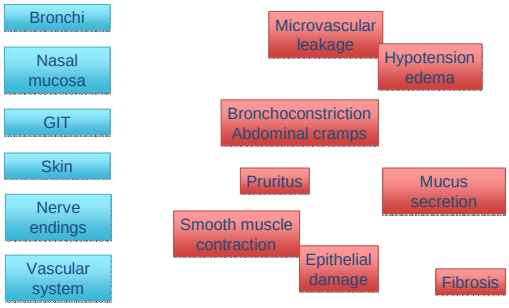


Larche et al. 2006
Romagnani, 2004
Akdis, 2006



vasoactive amines-histamine
lipid mediators-PGD, PAF, LTC4, LTD4 and LTE4,
chemokines-CXCL8, CXCL10, CCL2, CCL4 and CCL5,
cytokines- IL-4, IL-5 and IL-13

Roles of Mediators



IL-4

Stimulates activated B-cell & T-cell proliferation

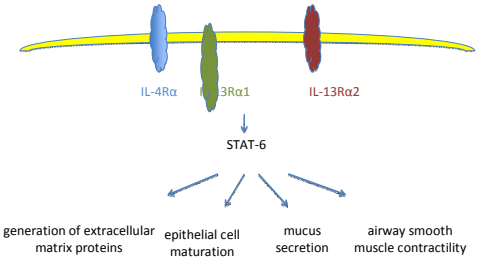
induce class switching

up-regulates MHC-II

www.wikipedia.org

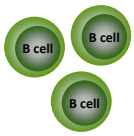
IL-13 exerts similar biological properties as IL-4
functions through IL-4Rα
shares common signaling pathways

IL-13



Kasaian and Miller, 2008
Wills-Karp, 2004
Elias, 2003

IL-5

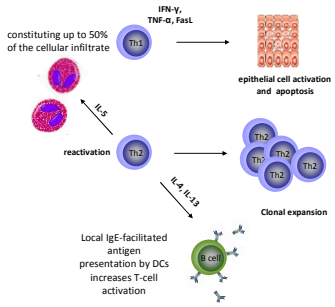


B cell growth

Activator of eosinophils

Sehmi et al. 1992

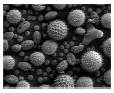
Late phase of the allergic reaction



chronicity

Major allergens

- Aeroallergens
- Foods
- Medications
- Latex
- Insect venoms



Type-1 hypersensitivity rxn

www.wikipedia.org

AVOIDANCE

Strickly IMPOSSIBLE

Pharmacotherapy

- Anti-inflammatory
- Relievers
- mAbs

Allergen specific immunotherapy

Allergen specific immunotherapy

- Repeated administration of sensitizing allergen
- Disease modifying / not only palliative
- Long duration of action
- Prevent new onset of sensitizations
- Reduce the development of asthma in AR pts
- Improves QoL

Moller et al. 2002
Des Roches et al. 1997

Routes of SIT

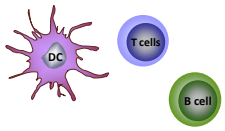
- Conventional-SCIT
- Oral-early 1900s
- Local bronchial-1950s
- Nasal-1970s
- SLIT-1986-first DBPC-Scadding GK et al.
- Intralymphatic trials

Mechanism of action of SIT-
incompletely defined

- Heterogeneous
  - allergen preparation
  - treatment protocol
  - routes
  - outcome measures

SIT modifies responses of

- APC
- T cell
- B cell
- Effector cell



- Induce of regulatory T cells
- Produce of blocking-antibodies
- Suppress of effector cell functions

Larche, Akdis, Valenta*Nature Reviews* 2006

Effects of SIT on APC

SIT → partially mature DCs → Toleregenic interaction with T cells

immature DC induce TReg cells (Tr1)

partially mature DC express IL-10 & induce Tr1

Jonuleit H et al. J Exp Med 2000
Akbari O et al. Nature Immunol 2001

Regulatory T cells

nTReg

naturally occurring
thymus selected
CD4+CD25+Foxp3+

Tr1

Adaptive-inducible
IL-10 secreting Tr1
TGF-β secreting Th3 cells.

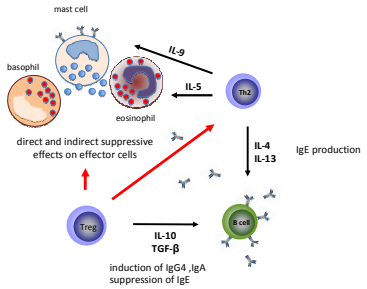
IL-10

- An anti-inflammatory cytokine ???
- Down-regulate MHC-II & co-stimulatory molecules
- enhances B cell survival, proliferation, and antibody production
- can block NF-kB activity
- Involved in JAK-STAT signaling pathway

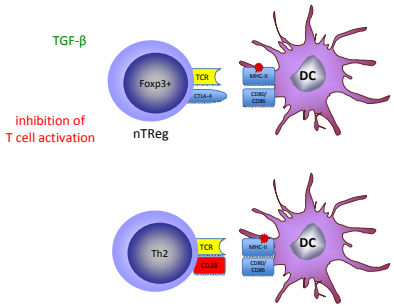
TGF-β

- Expansion of CD4+CD25+ cells,
- Induce Foxp3
- GATA3-driven Th2 responses inhibit TGF-β induced Foxp3 expression

Huber et al. 2004
Chen et al. 2003
Ouaked et al. 2009
Mantel et al. 2007



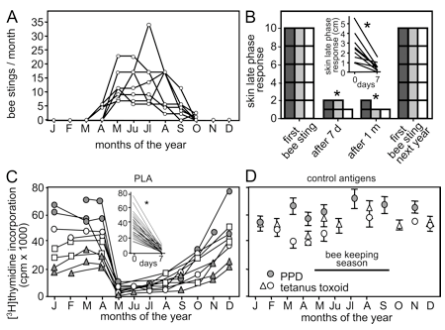
CTLA-4 compete with CD28 for CD80/86 ligands and thereby inhibit the costimulatory effect of CD28.



nTReg express CTLA-4,
CTLA-4 inhibits T cell activation in contrast to CD28.

influence of SCIT on T cells

- generation of allergen-sp-TReg cells
- induction of peripheral tolerance
  - suppresses proliferative and cytokine responses against the responsible allergens
- increased IL- 10 in allergen-stimulated peripheral T cell cultures

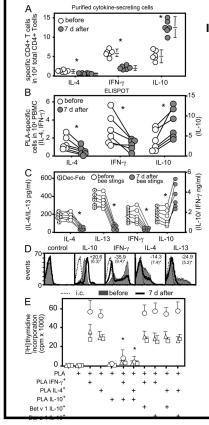


Beekeepers

Continuous exposure to PLA

induces diminished T cell–related cutaneous late-phase swelling
suppressed allergen-specific T cell proliferation

Meiler F et al. J Exp Med 2008;205:2887-2898



Increased allergen-specific Tr1 cells and decreased Th1 and Th2 cells after bee stings.

Suppressed Th1 & Th2 cytokine secretion.

After multiple stings, PLA-sp-Th1 and Th2 cells show a switch toward IL-10–secreting Tr1.
T cell regulation continues as long as antigen exposure & returns to initial levels within 3 mo

Meiler F et al. J Exp Med 2008;205:2887-2898

- skewing to Th1 type local nasal T cell response
- nasal mucosal
  - IL-10,
  - TGF-β,
  - Foxp3+ Treg

Durham SR et al. JACI1996
KlimekL,et al. CEA 1999
Radulovic S, et al. JACI 2008

SCIT-antibody responses

- transient increases in allergen specific IgE,
- blunting of seasonal increases in IgE,
- increases in sp-IgG, IgA,
- inhibit allergen-IgE binding to B-cells

Nouri-Aria KT et al. J Immunol 2004
Niederberger V et al. PNAS USA 2004
Jutel M et al. Eur J Immunol 2003.
Pilette C et al, J Immunol 2007.

Blocking antibodies

- Reduce IgE mediated degranulation of mast cells &basophils
- Reduce acute respiratory symptoms of allergic disease
- Attenuation of seasonal IgE increases
- Inhibits IgE facilitated allergen presentation to T cells (decreasing late-phase rxns)
- Reduce memory B cells

IgG4

- can block IgE-mediated histamine release
- competes with IgE for allergen-*block access of allergenic proteins to targets*
- stimulate surface IgG-inhibitory receptors of basophils and mast cells
- levels do not correlate with the clinical outcome

IgA

- unable to block allergen-IgE binding to B cells
- releases IL-10

Effects on effector cells

- Decrease in the numbers at mucosal sites,
  - Th2 and Eos decrease at the sites of allergen challenge
  - reduce Mast cells in skin
- reduction effector cell reactivity in vitro

Wilson et al. CEA 2001
Mother et al. CEA 2003
Furin et al. ClinImmunol 1991

Limitations

Sublingual immunotherapy

Sublingual immunotherapy-SLIT

- similar immunological mechanisms
- magnitude of changes in parameters is moderate
- IgG4 & IgA increased
- modest increases in sp-IgG4 and IgE blocking activity
- decrease of IgE/IgG4-not consistently observed

Sublingual immunotherapy-SLIT

- reduced proliferation of peripheral blood T cells
- better safety profile-anatomical- fewer mast cells- delivery of smaller immunologically active allergen doses
- increase in peripheral T cell IL-10, decrease in IL-4, TNF-α and IFN-γ

[Fenoglio et al. 2005]
[Di Gioacchino et al. 2008]

Sublingual arena

- site of tolerance induction
- network of LCs, epithelial cells &monocytes capable of producing IL-10,TGF-β
- daily contact to huge number of dietary antigens
- retention of allergen in sublingual mucosa for several hrs

[Alpan, 2001; Alpan et al. 2001; Friedman, 1996].

Oral cavity

- various subsets of tolerogenic DCs in a compartmentalized manner and programmed to induce Th1/Treg responses.
  - mDCsare present in the mucosal/submucosal interface,
  - pDCs-in submucosa
  - LCs-in mucosa-a minor subset
- contact-lack of inflammatory cell recruitment
- secretory IgA have an anti-inflammatory effect

[Allam et al. 2003]
[Mascarell et al. 2008]

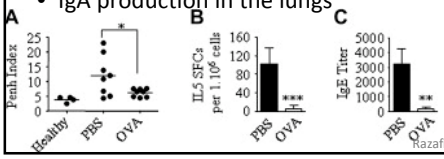
Analysis of kinetics

- radio-labelled purified *Parietaria*(Par j 1)
  - labelled allergen- rapidly degraded &absorbed in GIT after swallowing,
  - radioactivity associated with the oral mucosa remained for up to 18-20 hrs.

[Bagnasco et al. 1997].

Prolonging and facilitating

- OVA with a mucoadhesive formulation/ maltodextrin improved AHR & lung inflammation in a murine SLIT model.
- Increases in OVA-sp T-cell proliferation in cervical but not mesenteric lymph nodes
- IgA production in the lungs

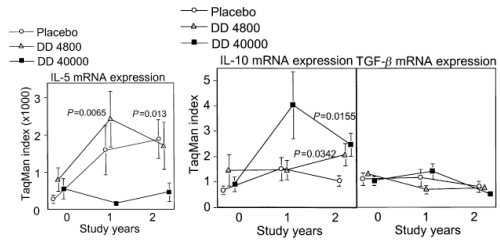


Razafindratsita et al. 2007

SLIT induces Tregs

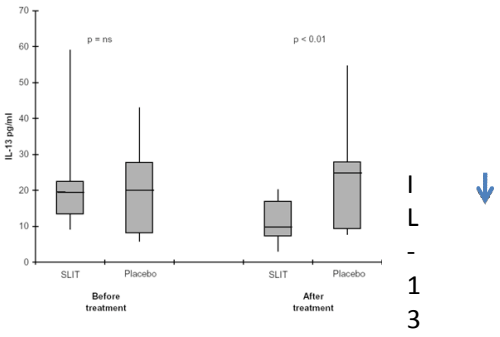
- HDM
  - reduced T-cell proliferation
  - peripheral IL-10 production
- Birch
  - CD4+CD25+ T cells have been detected, together with increasedFoxP3 & IL-10 and reduced IL-4 and IFN-γ expression.
- proliferative responses to antigens are decreased

Ciprandi et al. 2005
Burastero et al. 2008



High-dose SLIT course decreases IL-5 expression in an inverse correlation with TGF-β levels

[Savolainen et al. 2006].



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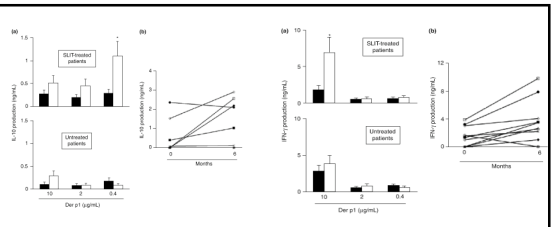
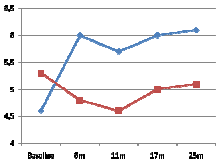
Ippoliti et al. PAI 2003



downregulates allergen-specific immunoglobulin E and increases both IL-10- and IFN-γ production

Cosmi et al. 2006

Modulation of allergen-specific antibody responses



in HDM asthmatics (DBPC) - significant increase in IgG4 levels after SLIT [Bousquet et al. 1999].

Der-p-IgG4

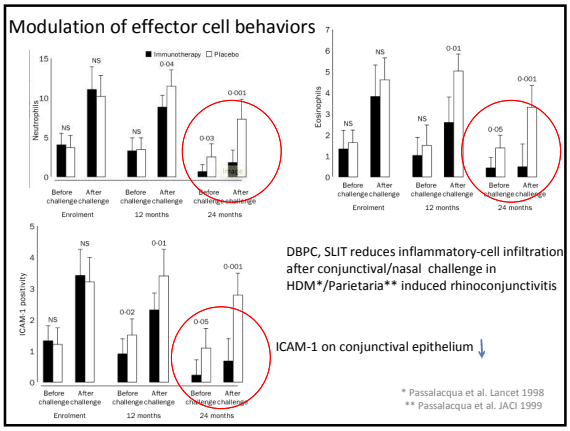
- Marked IgG4 increase in grass pollen extract in rhinitis (DBPC) [Clavel et al. 1998].

- In a 6-month course of a sublingual-swallow immunotherapy regimen in grass pollen allergic patients with AR, a significant increase in specific IgG4 and IgG4/IgE compared with treatment with placebo was observed
- impact of SLIT on IgE levels-conflicting data

Tseng et al. 2008

Ozdemir et al. 2007
Calamita et al. 2006
Tari et al. 1994

Modulation of effector cell behaviors



DBPC, SLIT reduces inflammatory-cell infiltration after conjunctival/nasal challenge in HDM*/Parietaria** induced rhinoconjunctivitis

ICAM-1 on conjunctival epithelium ↓

* Passalacqua et al. Lancet 1998
** Passalacqua et al. JACI 1999

Successful SIT

- increases in allergen-specific serum antibodies (particularly IgG1 and IgG4 and, to a lesser extent, IgA).
- proliferative responses of T cells to allergens are reduced,
- cytokine-secretion profiles are modified, resulting in an increased ratio of Th1-cell responses to Th2-cell responses
- functional Treg cell induction.
- Treg cell function & changes in serum-antibody profiles seem to be associated with expression of IL-10 and TGFβ.

Still questions

- efficacy in disorders other than asthma & AR
- optimal dose& duration
- optimal age to start
- any adjuvant or in combination
- other routes