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

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Burden of allergic disorders increase

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

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
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

Tolerogenic function

- capture and engulf
- interact with T and B cells
- initiate and shape the adaptive immune response
Cytokines are involved in the regulation of immune responses and inflammatory processes. For instance, IL-12, produced by dendritic cells (DCs), can stimulate the differentiation of Th1 cells, which produce IL-2 and other cytokines. In atopy, different cytokines such as IL-4 and IL-13 play crucial roles in the Th2 bias, leading to allergic reactions and asthma.

**Roles of Mediators**
- **Bronchi**: Microvascular leakage, hypotension, edema
- **Nasal mucosa**: Bronchoconstriction, abdominal cramps
- **GIT**: Pruritus, mucus secretion
- **Skin**: Smooth muscle contraction, epithelial damage, fibrosis
- **Nerve endings**: Vascular system

**IL-4**
- Stimulates activated B-cell & T-cell proliferation
- Induce class switching
- Up-regulates MHC-II

**IL-13**
- Up-regulates MHC-II
- Stimulates airway smooth muscle contractility
IL-5

- Activator of eosinophils
- B cell growth

Late phase of the allergic reaction

- Chronicity
- Activated eosinophils and mast cells
- Late phase Th2 response
- IL-5 constituting up to 50% of the cellular infiltrate

Major allergens

- Aeroallergens
- Foods
- Medications
- Latex
- Insect venoms

Type 1 hypersensitivity reaction

Pharmacotherapy

- Anti-inflammatory
- Relievers
- mAbs

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

### 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

### 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

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

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

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

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

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
• stimulates 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

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 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

Oral cavity
- various subsets of tolerogenic DCs in a compartmentalized manner and programmed to induce Th1/Treg responses.
  - mDCs are 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

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.
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

SLIT induces Tregs

- HDM
  - reduced T-cell proliferation
  - peripheral IL-10 production
- Birch
  - CD4+CD25+ T cells have been detected, together with increased FoxP3 & IL-10 and reduced IL-4 and IFN-γ expression.
  - proliferative responses to antigens are decreased

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

Modulation of allergen-specific antibody responses

- 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

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