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Mechanisms of Sub-Lingual Immunotherapy

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Allergen-specific Immunotherapy

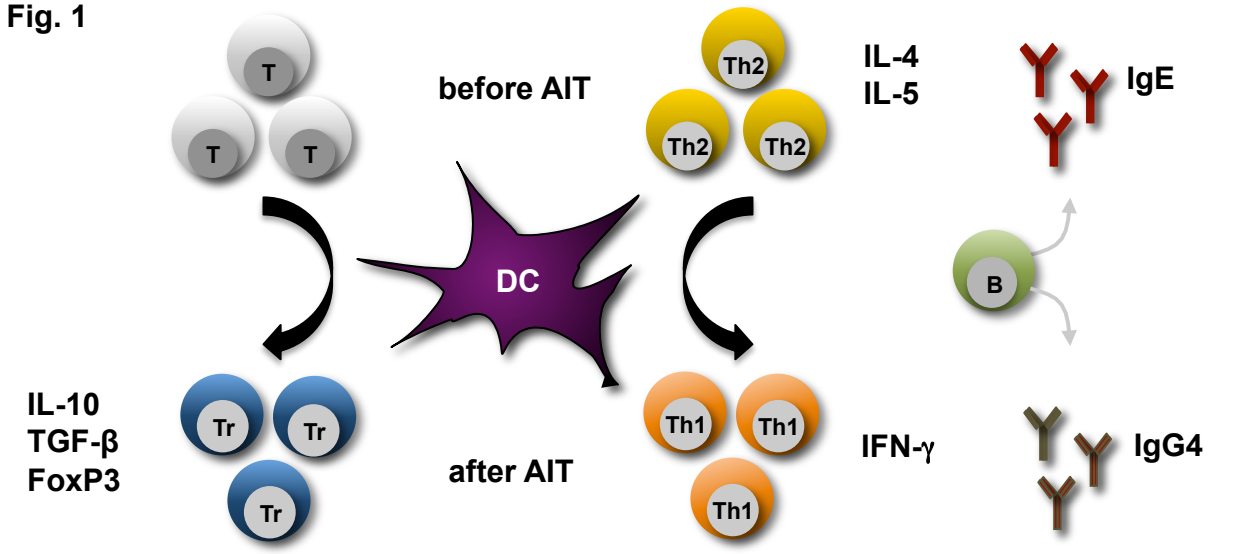
To date Allergen-specific immunotherapy (AIT) represents the only causal therapy in the treatment of IgE-mediated allergies such as allergic rhinitis or mild asthma [1]. The traditional form of AIT includes repetitive subcutaneous injection of allergens and is referred to as subcutaneous immunotherapy (SCIT). The clinical efficacy of SCIT has been confirmed by many placebo-controlled studies and it represents daily routine in allergy treatment [1]. However, severe systemic adverse reactions in SCIT such as anaphylaxis and its invasive character and relatively time consuming character advanced the search for alternative allergen delivering strategies. In this context oral mucosal surfaces such as sublingual mucosa have been investigated for alternative allergen administration [2]. Recent systematic reviews could demonstrate safety and efficiency of sublingual immunotherapy (SLIT) in the treatment of allergic rhinitis as well [3-6].

Notes

Current concept of immunotherapy

Although detailed immunological mechanisms underlying AIT have not been elucidated, the current concept postulates a shift from an allergy accelerating Th2 to an allergy protecting Th1 immune response along with an increase of allergen-specific IgG4 and decrease of allergen-specific IgE [1,7]. Further on, recent publications suggest a critical involvement of tolerance induction in response to AIT mediated by FoxP3(+) T regulatory cells (Tregs) or Transforming Growth factor (TGF)-β1 and/or interleukin (IL)-10 producing regulatory T cells [8]. Nonetheless, it is most likely that antigen presenting cells (APCs) such as dendritic cells (DCs) play a critical role, as DCs are essential for the initiation and modulation of T cell immune responses [9] (Fig. 1).

Fig. 1

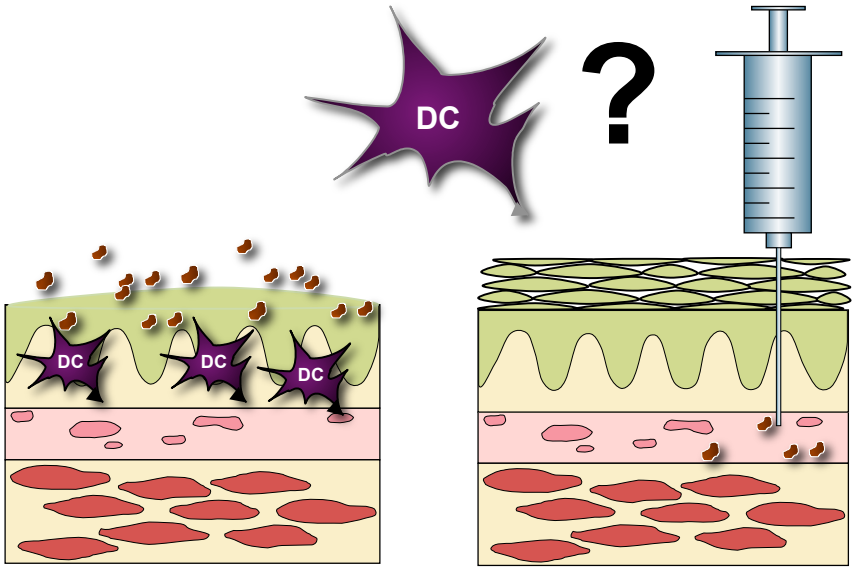


Notes

DCs in SCIT and SLIT

While the critical DCs population for allergen uptake during SCIT remains completely unknown, it is more than likely that resident DCs within the oral mucosal epithelium or lamina propria mucosa bind allergen during resorption during SLIT [9] (Fig. 2).

Fig. 2

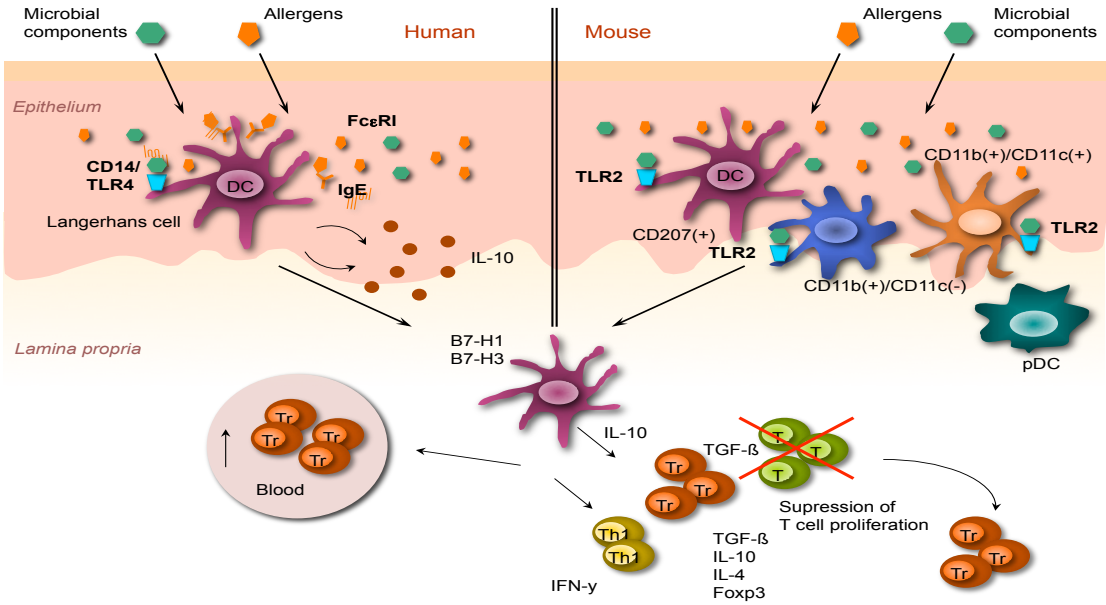


Notes

DCs in SLIT

Among different resident DCs within the murine oral mucosa, CD11b(+)/CD11c(-) and CD11b(+)/CD11c(+) DCs located at the mucosal/submucosal junction play a critical role in antigen uptake during resorption [10]. In contrast to mice, classical CD1a(+)/CD207(+) Langerhans cells (LCs) represent the major DC population within human oral mucosa, which constitutively expresses the high affinity receptor for IgE (FcεRI) next to innate immune receptors such as TLR4 [11]. Activation of TLR4 on oral LC (oLCs) led to an upregulation of co-inhibitory molecules B7-H1 and B7-H3 as well as the induction of IL-10 production by LCs underlining their pro-tolerogenic character. Moreover, ligation of TLR4 on human oLCs induced FoxP3(+) Tregs producing IL-10 and TGF-β1 along with IFN-γ producing Th1 cells in vitro. Further on, data from a BALB/C mouse model could also demonstrate induction of theTh1 cytokine IFN-γ and protolerogenic cytokine IL-10 producing Th1/regulatory T cells in response to sublingual ovalabumin challenge. In humans, it has been shown recently that oLC bind the major grass pollen allergen Phleum pratense (Phl p 5) in a time and dose dependent manner which resulted in an enhancement of their pro-tolerogenic properties [12] Altogether, recent data could show that oral mucosal DCs process antigens applied on mucosal surfaces and that these DCs are able to enforce tolerogenic mechanisms [9](Fig. 3).

Fig. 3



Conclusion

• SLIT represents a safe an effective rationale-based long time treatment for allergic rhinitis.

• Oral mucosal DCs bind and take up locally applied allergen/antigen.

• Activation of oral mucosal DCs enforces their tolerogenic properties.

• Oral mucosal DCs induce regulatory T cells as well as Th1 cells.

• SLIT preferentially induces a regulatory and Th1 immune response.

Questions to be answered:

• Elucidate detailed immunological mechanisms of SLIT and SCIT.

• Identify receptors on oral mucosal DCs, which bind allergen during SLIT.

• Identify receptors on oral mucosal DCs, which might enhance allergen binding and serve as targets for adjuvants.

• Oral mucosal regions with optimal allergen resorption and high numbers of DCs.

Bottom line:

• Provide optimal and safe care for allergic patients.

Notes

Further reading:

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