Human apolipoprotein C1 transgenic mice: a unique model of atopic dermatitis

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Background

Atopic dermatits is a skin disorder which affects 5-20% of the population in the Western countries. Treatment is largely confined to the application of anti-inflammatory drugs, such as corticosteroids and calcineurin inhibitors. Because such treatments show transient effects and do not mediate long-lasting effects, there is a great need of drugs that interfere with initial triggers of the disease. Appropriate animal models are essential for the identification of potential drugs. Here, we describe a model of atopic dermatitis that develops spontaneously in mice transgenic for human apolipoprotein C1 (APOC1).

Materials and methods

- Human APOC1 transgenic mice were developed as described previously (Jong et al., J Clin Invest 101, 145-152, 1998) to study the effects of its overexpression on lipoprotein metabolism. For the study of atopic dermatitis a breeding colony was established employing female APOC1+/- and male APOC1+/+ mice.
- Measurements of epidermal hyperplasia and the enumeration of eosinophils and neutrophils were performed after staining of fixated tissue sections (5 µm) with hematoxyllin/eosin/saffran. Numbers of mast cells were assessed after toluidin blue staining.
- $CD4^+$ or IgE^+ cells were studied by the staining of cryosections with anti-CD4-biotin or anti-IgE-biotin, followed by incubation with HRP-labeled streptavidin, and using AEC as a substrate.
- Transepidermal water loss was measured with the use of a TM210 TEWAmeter.
- Pruritus measurements were performed for individual mice employing a Laboras system. Movements with a frequency between 5 and 25 Hz and a duration of at least 0.2 sec were found to reflect a scratch event.

Results

- Homozygous APOC1+/+ mice gradually develop symptoms of dermatitis evident from increased scaling, papules, lichenification and excoriations (**Figure 1**). Progression of disease is associated with spongiosis (not shown). APOC1+/- mice remain free of symptoms (data not shown).
- Histopathology of the lesions reveals both epidermal and dermal hyperplasia (**Figure 2**) with an early involvement of eosinophils , mast cells and CD4+ T cells. At early age eosinophils outweigh the number of neutrophils; however, the latter increase in numbers and become more prominent at later age (**Figure 3**).

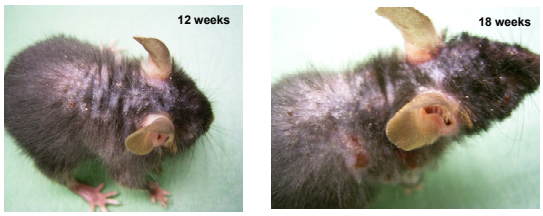

Fig. 1 Atopic dermatitis in APOC1+/+ mice

- **Figure 3** shows a gradual increase in numbers of mast cells when the mice grow older (open symbols reflect APOC1+/- and wildtype mice).
- Importantly, APOC1+/+ mice have increased serum IgE levels from an age of 10 weeks onwards and subsequently show IgE+ mast cells in the dermis (**Figures 2 and 4**).
- Development of atopic dermatitis may be the consequence of a disturbed skin barrier as measured by increased trans epidermal water loss (**Figure 5**).
- Atopic dermatis in APOC1+/+ mice is associated with the development of pruritus (**Figure 6**).
- Inflammation and epidermal hyperplasia are suppressed by corticosteroid treatment (**Figure 7**).

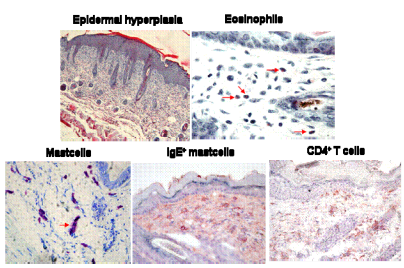

Fig. 2 Epidermal hyperplasia and inflammatory cells in APOC1+/+ mice

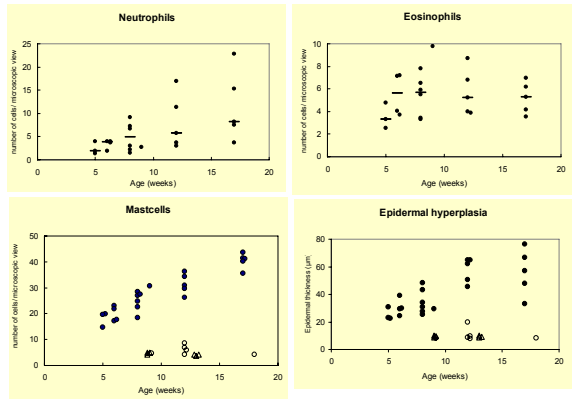

Fig. 3 Epidermal hyperplasia and inflammatory cells in APOC1+/+ mice

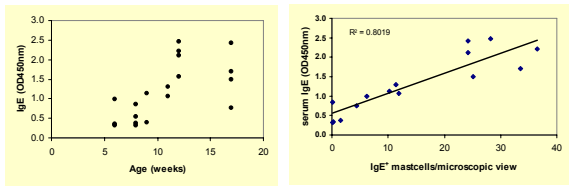

Fig. 4 Increased serum IgE levels are reflected by IgE^+ mast cells in the dermis

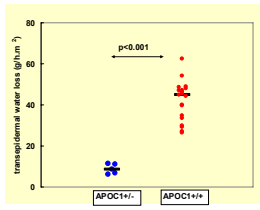

Fig. 5 APOC1+/+ mice show a disturbed skin barrier function, evident from increased trans epidermal water loss.

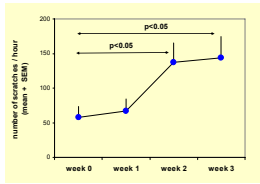

Fig. 6 : Development of atopic dermatitis is associated with increased pruritus. Mice with a severity of dermatitis, ranging from 3 to 5 on a 9-point severity scale were included. Individual mice were monitored weekly.

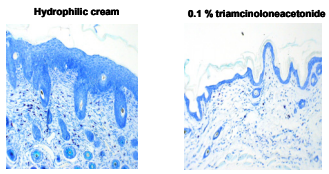

Fig. 7 : Atopic dermatitis in APOC1+/+ mice is sensitive to corticosteroid treatment. APOC1+/+ mice were treated for a period of 3 weeks by topical application from an age of 9 weeks onwards.

Conclusions

- APOC1+/+ mice develop atopic dermatitis; various features are suggestive for a Th2-mediated mechanism, i.e. the involvement of eosinophils, mast cells and IgE.
- Symptoms of atopic dermatits develop gradually and are associated with increased pruritus.
- APOC1+/+ mice have increased transepidermal water loss, which can already be detected at an age of 6 weeks; possibly, this enables the activation of the immune system by a trigger which favors a Th2-mediated mechanism
- Various aspects of atopic dermatitis are sensitive to triamcinolone-acetonide; in addition, topical application of fluticasone or tacrolimus and oral administration of dexamethasone were found to suppress symptoms of atopic dermatitis in this model (data not shown).