mice express seven different LOX-isoforms. Functional inactivation of the different genes induced different

Cytokine-dependent Expression Regulation of Human *ALOX15*

IL4- and IL13-dependent expression regulation of *ALOX15* in human monocytes

In human circulating blood monocytes *ALOX15* is not expressed. However, when these cells were cultured *in vitro* in the presence of recombinant human IL4 (60-600 pM, which corresponds to 0.9-9 ng/ml) for 3 days *ALOX15* expression was strongly upregulated as indicated by immunohistochemistry, Northern blotting and activity assays [16]. The induced enzyme reacted with endogenous substrates since specific *ALOX15* products (15S-HETE) were detected in the membrane lipids. IL4-dependent *ALOX15* expression was time-dependent and maximal induction was reached after

ALOX15 [108]. Transforming growth factor beta1 counteracted the IL4-dependent suppression of ALOX5 expression but did not alter *ALOX15* expression. These findings were consistent with the results of metabolomic studies, which indicated that in the absence of IL4 5-HETE and leukotriene B4 were the major eicosanoids produced by dendritic cells derived from CD34-positive precursors. In contrast, 15-HETE and 5S,15S-diHETE were the major eicosanoids formed in the presence of IL4. These data indicate that dendritic cells, which were transdifferentiated from peripheral monocytes *in vitro* in the presence of IL4, express large amounts of *ALOX15* [108]. However, it remains to be explored whether this effect is of any *in vivo* relevance. For the time being there is no convincing experimental evidence that *in vivo* differentiated dendritic cells express large amounts of *ALOX15*.

Orbital fibroblasts

antibodies confirmed the physical interaction of the Ku antigens with the *ALOX15* promoter and electroporation of neutralizing anti-Ku antibodies into A549 cells suppressed IL4-induced *ALOX15* expression [121].

As indicated above, IL4 has been related to the energy metabolism of adipocytes [114]. AMP- activated protein kinase (AMPK) is a key enzyme in the energy metabolism of all cells [122] but until recently no connection between IL4-dependent induction of

Figure 3: Comparison of the IL4 plasma levels of patients suffering from allergic diseases. T e

Interestingly, there was no difference in the *ALOX15* activity of these two cell preparations and these data indicate that IL4 is not required for constitutive expression of this enzyme in mouse macrophages.

Open questions and perspectives

The classical T2 cytokines IL4 and IL13 are powerful inducers of *ALOX15* expression in human [16,17] and mouse peripheral monocytes [132], although in mice constitutive expression of this enzyme in peritoneal macrophages is not IL4-dependent [133]. A number of other cytokines including IL1, IL2, IL3, IL4, IL5, IL6, IFNg,

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