

The impact of PPAR and LXR signalling on Alzheimer's disease

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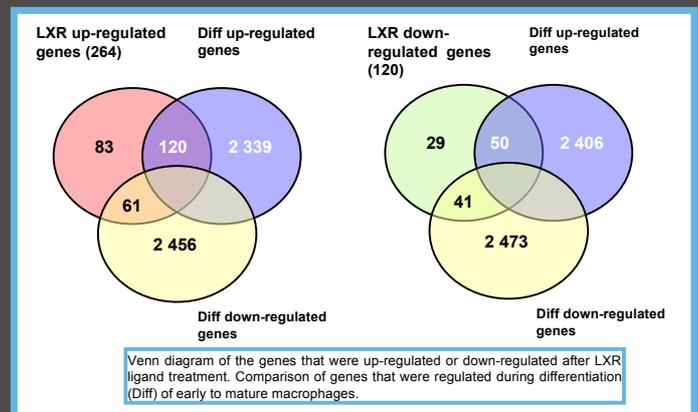
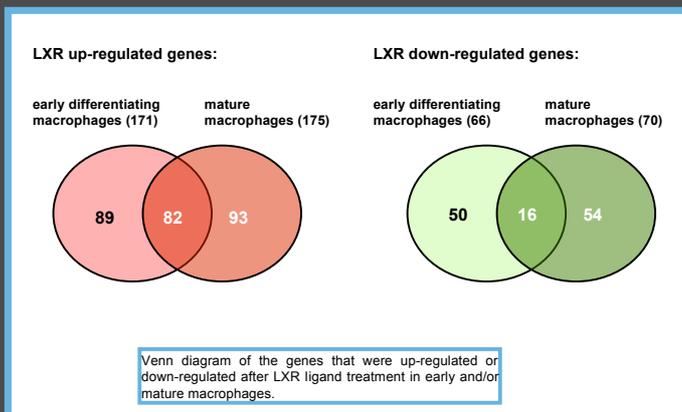
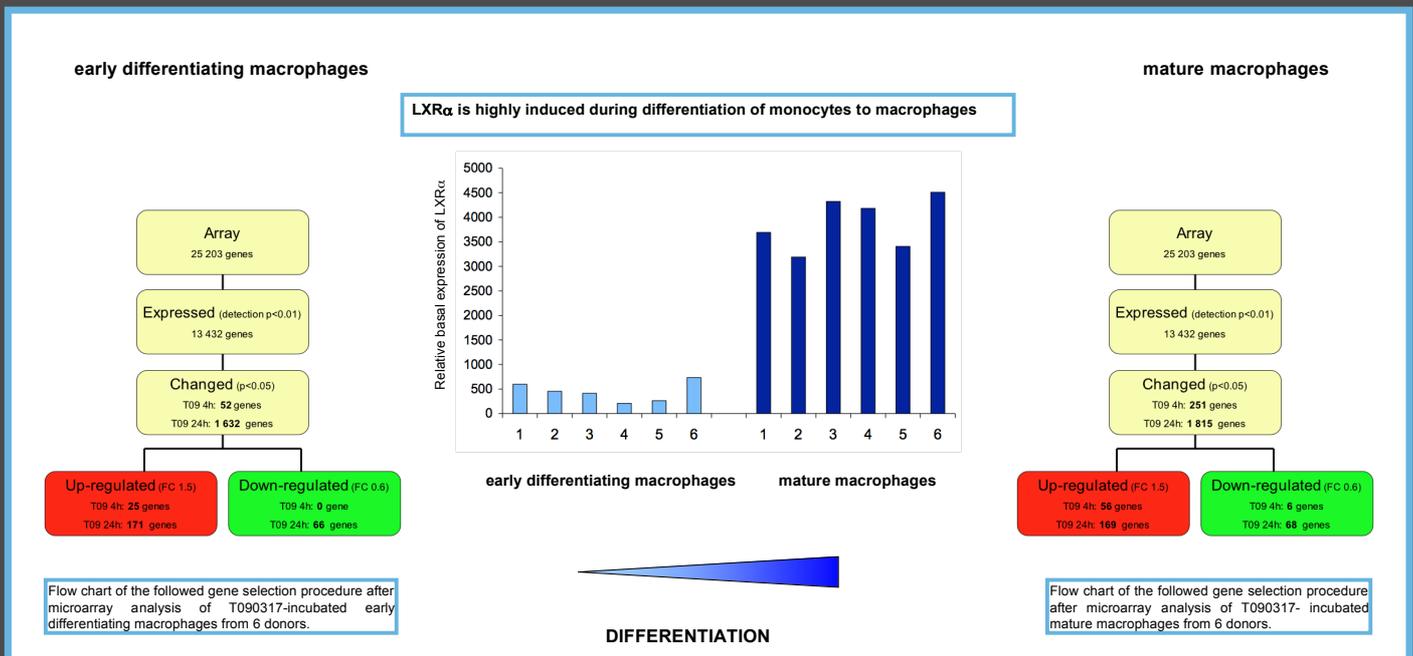


1 - Background

Alzheimer's disease (AD) is an age-dependent neurodegenerative disease that causes progressive cognitive impairment. The initiation and progression of AD has been linked to cholesterol metabolism and inflammation, processes that can be modulated by peroxisome proliferator-activated receptor-gamma (PPAR γ) and liver X receptor (LXR). PPAR γ and LXR are ligand-activated transcription factors that belong to the superfamily of nuclear receptors. The activation of these transcription factors have been associated with potent anti-inflammatory as well as anti-amyloidogenic effects in cell culture and AD animal models. Unfortunately, very little is known about the molecular mechanisms that subserve these effects. We believe that unraveling the molecular mechanism of these neuroprotective effects is of central importance for the understanding of the pathogenesis of AD. In AD brains, the resident macrophage population, the microglia cells release elevated levels of inflammatory mediators and are defective in the clearance of amyloid- β deposits. These inappropriate microglia functions are postulated to contribute to neuronal degeneration and cell death in AD patients. Pharmacological modulation of microglia/macrophage gene expression therefore represents an important therapeutic approach for the treatment of AD.

We are currently evaluating the effects and consequences of PPAR and LXR activation on monocyte/macrophage differentiation and activation. Here we present the genome-wide expression analyses of LXR-treated early differentiating and fully differentiated macrophages. Global gene expression profiling was performed using Illumina GeneChips and data were obtained from 6 biological replicates.

2 - Results



3 - Discussion-Conclusion

Taken together, in this study we characterized the gene-expression pattern of LXR-activated early differentiating and mature macrophages. We observed that PPAR γ and LXR α is highly induced during differentiation of monocytes to macrophages. More than 230 genes are regulated in early as well as mature macrophages by activation of LXR; most of them are up-regulated. These changes appear to modulate the genes expression profile associated with macrophage differentiation. In early differentiating macrophages only genes related to lipid and cholesterol metabolism are overrepresented among early induced genes. In contrast, genes related to immune function, cell morphology and cell proliferation respond at later time points. In contrast, in mature macrophages showing high LXR expression, some of the same functional gene clusters respond far earlier after LXR ligand treatment.

In conclusion, our data suggests that LXR are modulators of macrophage differentiation, acting mostly as positive transcriptional regulators of genes involved in lipid and cholesterol metabolism, as well as genes associated with immune function, morphology and proliferation. The molecular details of the links between lipid metabolism, immune function and proliferation remain to be investigated but clearly some of the novel identified primary LXR and PPAR targets increase our understanding of the control of macrophage/microglia functions by these transcription factors.