Nuclear receptors modulate immune functions in dendritic cells

The case of vitamin D receptor and the regulation of immune function-related genes

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SUMMARY

Dendritic cells (DCs) are conductors of the adaptive immune system with a capacity to activate naive T-cells and regulate their functions. The integration of environmental signals will lead to at least two distinct, immunogenic and tolerogenic, DC immunophenotypes. How these stereotypic immunophenotypes are achieved at the transcriptional level is not well understood. A member of nuclear hormone receptor family, vitamin D receptor (VDR) is implicated in the development of tolerogenic DC phenotype. We have performed microarray studies to identify transcriptional programs regulated by VDR, retinoic acid receptor α (RARα) and the differentiation process in developing DCs. Using these datasets we aimed at clarifying the connection of the VDR-coordinated program to the differentiation process as well as to the RARα-regulated transcriptional program.

(1) Previous studies suggested that 1,25-dihydroxyvitamin D_3 (1,25-vitD) could inhibit the changes brought about by differentiation and maturation of DCs. However, it has not been explored how 1,25-vitD-regulated genes, particularly the ones bringing about the tolerogenic phenotype, are connected to differentiation. Using the global gene expression analysis followed by comprehensive quantitative PCR validation we could clarify the interrelationship between 1,25-vitD and differentiation-driven gene expression patterns in developing human monocyte-derived and blood myeloid DCs. We found that 1,25-vitD regulates a large set of genes that are not affected by differentiation. Interestingly, several genes impacted both by the ligand and by differentiation, appear to be regulated by 1,25-vitD independently of the developmental context. Our data collectively suggest that exogenous or endogenously generated 1,25-vitD regulates a large set of its targets autonomously and not via inhibition of differentiation and maturation, leading to the previously characterized tolerogenic state.

(2) In our ongoing study we have shown that RARα and VDR initiated similar phenotypic and functional changes. Using microarray analysis we have found that ~50% of 1,25-vitD regulated genes were also regulated by AM580 (RARα agonist) at the late stage of DC differentiation. We aim at identifying the potential molecular mechanisms that may be responsible for this phenomenon. Most importantly, we would like to identify target genes that are regulated by the same response elements of the two receptors.

Keywords: Nuclear receptor, dendritic cell, vitamin D

Kulcsszavak: magreceptor, dendritikus sejt, D-vitamin