INVESTIGATION OF THE MONOCYTE DERIVED DENDRITIC CELLS' DIFFERENTIATION AND ACTIVATION

Dendritic cells represent a diverse group of cells with various properties and origin. Their main common property is the efficient influence on other cell types, especially on the function and the differentiation of the naïve T lymphocytes. The properties of the dendritic cells achieved by their differentiation and activation can direct the mounted immune response. With the appropriate knowledge of these processes, the direction of the immune response (e.g. the suppression or the boost) can be influenced according to our need by the manipulation of the dendritic cells.

Our group has been examining the human monocyte derived dendritic cells which can be considered to a subtype of the inflammatory dendritic cells. Monocytes can be differentiated to dendritic cells within days *in vitro* by the help of appropriate cytokines (GM-CSF and IL-4). Even these cells, which were differentiated in standard conditions, cannot be considered homogenous. According to the observations, at least two population is emerging during the differentiation. These two group can be easily distinguished by the presence or absence of the cell surface CD1a molecule, which belongs to the group of the MHC I-like, lipid presenting molecules, and which can be considered as a cell type "marker". The CD1a non expressing (CD1a−) population maintains some similarity with the original undifferentiated monocyte precursors. The CD1a− dendritic cells share some of their phenotypic properties with the monocytes, but they already express classical dendritic cell markers. They can produce large amount of anti-inflammatory IL-10 after their activation. In contrast, the CD1a expressing (CD1a+) cells can be considered as a real inflammatory dendritic cell population. They can produce IL-12, and higher amount of TNFα cytokines. They can polarise the differentiation of the Th1 cells more effectively.

In our experiments the differentiation of the monocyte derived dendritic cells was profoundly influenced by the presence of different materials in the cell culture medium. Cytokines, lipid containing materials, fatty-acids, but even the nutrient composition of the cell culture media have deep impact on the dendritic cells' differentiation. Some components from the supplemented lipoproteins in the cell culture medium can inhibit the appearence of the CD1a+ dendritic cells probably through the activation of the PPARγ nuclear receptor. Histamine can also decrease the appearance of the CD1a+ cells by the cell surface H2 receptors. Various autocrine effects should also be taken in consideration. Recently we have been examining a multifunctional autocrine antimicrobial neuropeptide, the adrenomedullin. This peptide also influences the differentiation and function of the dendritic cells. The adrenomedullin seems also inhibiting the differentiation of the CD1a+ cells.

The CD1a+ and CD1a− monocyte derived dendritic cells have different pattern recognition receptor garnitures, so different stimuli can act on them with different efficiency. We have shown that the CD1a+ dendritic cells possess viral sensor RIG-like helicases (RIG-I, MDA5), so they can be activated more efficiently in the presence of viruses or viral nucleic acid mimetics (polyI:C).

The ratio of the CD1a+ and CD1a− dendritic cells can be very different in the case of the monocyte differentation from different persons even in the case of the usage of very strict standardised procedures and cell culture reagents. In our experiments performed with standardised serum-free AIM-V medium the average ratio of the CD1a+ monocyte derived dendritic cells was 45%, with very broad donor-to-donor variance. We started to investigate the epigenetic effects as one of the possible causes of this large variance in the dendritic cell differentiation.