

The project relates to the studies of mast cell role in the induction and maintenance of inflammation. Mast cells are blood cells that do not circulate in the bloodstream but reside in various tissues where they perform functions of immune cells protecting the body against infection. A similar protective immune function perform type 17 T helper lymphocytes or Th17 cells that in contrast to mast cells circulate in the blood and lymph vessels.

When the immune system recognizes signals of danger at particular location in our body and initiates local inflammation both mast cells and Th17 are gathering there. Examples of sites of inflammation where there are many mast cells and Th 17 are joints of patients with rheumatoid arthritis (also called RA). The appearance of these cells is of major importance for the development of the disease because these cells produce and secrete into the surrounding tissues inflammatory mediators i.e. substances mediating multiple changes in surrounding tissues. If the inflammation persists for too long the changes induced by inflammatory mediators lead to disease symptoms such as morphological changes observed in cartilage and bones in rheumatoid arthritis. One of the important mediators of inflammation secreted by Th17 cells is protein called interleukin-17 (IL-17).

Although oxygen is essential to our life the concentration of oxygen in the atmosphere is toxically high for most cells in our organism. Inside the human body where cells have the optimal living conditions the oxygen concentration is substantially lower than atmospheric (21%) and ranges from 5% to 7%. Interestingly, in various tissues there is different oxygen concentrations and in inflamed tissue oxygen concentration is extremely low, and sometimes drops to zero. Most of the experimental studies on cells of the immune system such as lymphocytes and mast cells was so far carried out in the laboratory under normal atmospheric oxygen. Transferring cells to an atmosphere of reduced oxygen concentration that mimics conditions found in tissues including inflamed tissues causes some genes to be turned on and the other turned off changing cell phenotypes and thus changing cell function.

From our previous studies and scientific literature, we have learned that mast cells under hypoxic conditions acquire phenotype favoring the induction of inflammation. We have also learned that cultured human mast cells adhere to Th17 cells added to the same culture vessel, and occurrence of such adhesion event resulted in secretion of large amounts of IL-17 and other inflammatory mediators. However, we have observed this process under standard conditions in a normal oxygen atmosphere. In the research that we will carry out in this project mast cells will put in contact with Th17 cells under conditions of reduced oxygen that mimic conditions observed in inflamed tissues. Using this model, we will find genes and molecules that are necessary for adhesion of mast cells to Th17 lymphocytes. We will learn how the process of intercellular adhesion stimulates the production of inflammatory mediators. We will also find out if mast cells and Th17 cells interacting with each other under hypoxic conditions produce the same set of mediators of inflammation as in normal atmosphere. Finally, we will discover biological and pharmacological molecules capable to inhibit mast cell adhesion to Th17 and check whether inhibition of this adhesive process reduces the production of inflammatory mediators. Our studies will allow to discover a novel part of the molecular mechanism of chronic inflammation that when persist in the body causes some serious diseases.