Recognition of genes associated with H3K4me3 histone protein responsible for polarization of neutrophils into suppressor cells during refractory inflammatory diseases

Introduction

During evolution human body has developed a number of mechanisms leading to the elimination of invading pathogens. At the time of the invasion, immune cells recognize microorganisms and start their elimination. Many infections are eliminated by innate immunity mechanisms, without the active participation of specific response (acquired immunity). The innate immune system is characterized by very quick response, resulting in direct microorganism elimination by recognition of receptor constitutively expressed on the pathogens. Neutrophils, the main and most numerous cells that belong to innate immunity, are involved into pathogenesis of different diseases. As a first line of innate immune system, neutrophils play a key role in controlling antimicrobial immune response. Neutrophils are also pathologically activated during a range of autoimmune diseases, such as rheumatoid arthritis, diabetes mellitus or Devic disease. The effective management of inflammatory conditions of different origin is one of the major problems of current medicine. Although these diseases might have different pathogenesis, inadequate control of neutrophil function is an essential contributing factor of complications of many inflammatory conditions. Current anti-inflammatory treatment strategies based e.g. on conventional nonsteroidal anti-inflammatory drugs, selective inhibitors of the COX-2, or corticosteroids are associated with a risk of multiple systemic side effects, such as gastrointestinal mucosal injury, hypertension, dyslipidemia, thrombosis, peptic ulcers, gastrointestinal bleeding, osteoporosis, increased risk of infection, Cushing's syndrome, diabetes mellitus, adrenal atrophy.

Recently, neutrophils have been found to play a previously unsuspected suppressive role during acute and chronic microbial infection. Our previous studies have shown that T regulatory (Treg) cells play a crucial role in the regulation of deactivation of neutrophils, depending on whether they operate in septic or aseptic environment. Specifically, LPS-prestimulated Treg cells are the potent inducers of IL-10-producing apoptopic neutrophils, which, in turn, activate IL-10 production in other neutrophils and their massive apoptosis in the paracrine manner.

Significance

Determining the key genes responsible for the different status of neutrophils at the site of inflammation will enable to initiate the research into specific therapies helpful for treatment of refractory or life-threatening inflammatory conditions. We hope that our study will help to select the specific targets for the future therapies, for example pharmacological modulation of myeloid cell differentiation or gene therapy via siRNA or CRISPR sequences. Specific manipulation with myeloid cell genome might offer an effective tool to reverse unfavorable changes in neutrophils, providing better opportunity for effective antimicrobial treatment or neutralization of systemic activating factors, without the global effect on other immune cells resulting, as a side effect, in general immunosuppression.

Methodology

We are planning to employ the strategy used for searching for the cancer therapy, ‘from genes to the medicines’. First, we are going to analyze the differences at the level of genes, searching for candidate genes, next, analyze chosen genes at the level of mRNA expression. The comparison of DNA in the region of methylated histone H3K4me3, a major nucleosome undergoing remodeling under pro- and antiinflammatory factors, in neutrophils isolated from the patients with different diseases, where neutrophils are exposed to different stimuli, will allow to perform the first part of our research. Giving that there are only little individual-related differences in neutrophil genome, it might be assumed that changes in methylated histone H3K4me3 detected in our experiments, in comparison to the whole genome, are the result of different status of neutrophils during inflammation. Additional comparison of gene precursors between the patients with different diagnosis will help to select the genes responsible for polarization of neutrophils into pro- or anti-inflammatory cells, and will provide additional insight into cell function during different pathologies.