Development of Therapeutic Vaccines against IL-18 and Thymic Stromal Lymphopoietin (TSLP)

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Over the last 30 years, allergies have soared to almost epidemic proportions in the Western world. Current treatments use antihistamines, antileukotrienes or corticosteroids to fight allergy symptoms like sneezing, itching and asthma. In severe cases these symptoms can lead to anaphylaxis, cardiovascular collapse and death. In an attempt to target not only symptoms, but also earlier stages in disease development, the field of therapeutic vaccination has emerged. It potentially has the ability to target non-infectious diseases including allergy, autoimmunity, cancer, and also persistent infections like HIV. These vaccines target self-molecules and aim to reduce excessive amounts of important regulatory or inflammatory mediators. An allergic response can be dampened or even prevented, for example, by lowering the amount of certain host self-molecules. Earlier treatment strategies involved the use of monoclonal antibodies (mAb) aiming at similar molecular targets. However, these treatments are very expensive and may only be available in severe cases. Therapeutic vaccination is an interesting and more cost effective new addition to this field.

In this study I worked on the development of vaccines against two important regulators of allergic responses. The two molecules I have focused on are the cytokines interleukin-18 (IL-18) and thymic stromal lymphopoietin (TSLP), two regulators of immunoglobulin E (IgE) synthesis. Cytokines are signal molecules, which are produced by the majority of all cells and used for cellular communication. They are important regulators of host immune responses against many different antigens. IgE is the antibody class known for its central role in allergic reactions. Upon re-exposure to certain allergens IgE leads to the release of histamines, heparins, proteases and other inflammatory mediators, which in turn lead to the development of the previously mentioned symptoms.

Over time the immune system has evolved into a sophisticated machinery, which screens and destroys auto-reactive immune cells. In order to lower self-molecule amounts this self-tolerance must be overcome. One way to achieve this involves fusing a host molecule to a foreign antigen, which leads to the production of antibodies against this self-molecule.

I have optimized purification methods of fusion constructs for the cytokines IL-18 and TSLP. Such fusion proteins are used as vaccine antigens to break self-tolerance and induce antibody production against these cytokines, i.e. to lower their numbers. I explored different techniques for protein expression, refolding and purification in this study.

Finally, immunized laboratory rats given the vaccines were tested for their immune responses against the targeted self-molecules. Analyses showed significant antibody production against IL-18. First experiments to measure antibody responses, vaccine efficacy and safety showed promising results. However, due to time constraints, further testing for TSLP could not take place.