

Project description: Targeting of immunological memory

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State of the art

The adaptive immune system has the ability to preserve information over extended periods of time in the absence of instructive signals. This immunological memory is maintained by epigenetic and transcriptional imprinting and long-term survival of memory cells carrying this information. Immunological memory provides protection from recurrent infections, but it is detrimental in chronic inflammatory diseases, such as autoimmune diseases. While state-of-the-art immunosuppressive therapy is effective in preventing progression of disease, it does not provide a cure. The reason is probably because it does not target the immunological memory for the inflammation, which is independent of proliferation and costimulation. Complete immune ablation followed by rebuilding of a naive immune system from hematopoietic stem cells results in many cases in long-term therapyfree remission. This demonstrates that elimination of the pathogenic immunological memory can be curative in principle. On the other hand, in some cases the immune response is not sufficient to clear a pathogen or tumor cells, e.g. persistent viral infections or cancer, or immunization fails to lead to a protective immune memory. Here, there is a need to strengthen immune responses, by modulating physiological regulatory mechanisms, e.g. through regulatory T cells and inhibitory cytokines, and memory pool formation.

Aims

In the proposed project, the development of gene based modulation of immunological memory will be explored. The aim will be to target microRNAs and transcription factors playing an essential role in the expansion and survival of memory and effector/memory Th cells. Candidate target molecules for pathogenic Th effector/memory cells have already been identified and will be tested for their potential to modulate or eliminate pathogenic Th cells in murine models of chronic inflammation, such as the ovalbumin-induced arthritis and colitis models. Here, microRNA antagonist and siRNA approaches will be used to target the cells *in vivo*. The targets will be tested for their ability to stop inflammation during the acute and chronic phase of inflammation. It will also be analysed whether therapy of the chronic inflammation requires concomitant elimination of auto-antibody producing plasma cells and restoration of tolerance by regulatory T cells.

Similar approaches will be tested for their ability to strengthen immune responses and the development of immunological memory against pathogens by blocking molecules which limit the expansion and maintenance of reactive Th cells. Here, in collaboration with other groups of the GRAKO1121, targeting of such molecules in immune responses to various pathogens will be analyzed with regards to resolution of infection, limitation of immunopathology and establishment of protective immunity. In addition, understanding the molecular mechanism of regulation of clonal size and memory formation will allow targeted intervention in chronic infections with intracellular pathogens, possibly allowing the resolution of persistent infections.