Immune modulation by schistosomes: mechanisms of regulatory B cell induction and inhibition of allergic asthma

Obieglo, K.

Addendum &

ENGLISH SUMMARY

NEDERLANDSE SAMENVATTING

CURRICULUM VITAE

LIST OF PUBLICATIONS

ACKNOWLEDGEMENTS

ENGLISH SUMMARY

The immune system is our body's defence, protecting us from potentially harmful pathogens such as bacteria, viruses and parasites. It thereby has to differentiate between different microorganisms that can cause disease and should be expelled, and harmless substances that also enter the body but are not dangerous, such as food we eat or substances in the air we breathe. The immune system has developed a range of different responses, and most of the time mounts the appropriate reaction. Sometimes however, it fails to clear pathogens before they can do harm to the body, or it overreacts to harmless substances like pollen in the air or even or own body, causing e.g. asthma or autoimmune diseases. Asthma is a chronic inflammatory disease of the lung, which in characterized by symptoms such as breathlessness, chest tightness and wheezing. Allergic asthma, a common form of asthma and subject of this thesis, is caused by a reaction of the immune system to certain inhaled substances (allergens) such as dust mite or pollen.

The parasitic worm *Schistosoma* (commonly known as bilharzia), is a flatworm which can be found in freshwater snails and penetrates the host through the skin. Adult worms live and mate in the blood vessels of the intestine or bladder. There they lay eggs that are excreted with the faeces or urine. Worm parasites including *Schistosoma* are a unique class of parasites, as they usually remain in the human body for extended periods of time. These chronic infections do not only have adverse effects for the human host, but can in certain circumstances also be beneficial. Worms down-modulate the host immune response to promote their own survival, thereby providing protective effects against a spectrum of diseases with an overactive immune system, such as aforementioned asthma and autoimmune diseases. Worm parasites modify various aspects of the immune system, including the promotion of immune cells that act tolerogenic, such as regulatory B cells. While 'normal' B cells produce antibodies and protect us from invading microorganisms, regulatory B cells are immune cells that help to down-modulate the immune system when it is too active. A better understanding of how these cells get activated and how they work might enable us to make use of these cells for the treatment of e.g. asthma and autoimmune diseases.

Research conducted in this thesis

The first part of this thesis focusses on the role of regulatory B cells in protection from allergic asthma by chronic *S. mansoni* infections, as well as on the identification of molecular signals required for schistosome-induced development of regulatory B cells.

Chronic *S. mansoni* infection induces regulatory B cells both in the spleen and the lung. While splenic B cells are known to protect from allergic asthma by producing the immunomodulatory molecule interleukin (IL)-10, lung B cells act independent of IL-10. We further characterized these lung B cells with regulatory properties and show that they are phenotypically and functionally different from classical regulatory B cells in the spleen (**chapter 2**). This work therefore suggests the presence of distinct regulatory B cell subsets, even if induced by the same type of worm parasite.

Chronic *S. mansoni* infections are known to induce regulatory B cells. Single molecules that are produced and secreted by the worm to influence surrounding immune cells and mediate this protective effect had however not been identified yet. Moreover, the cellular mechanisms driving regulatory B cell development remained to be defined. We showed that a subset of B cells in the spleen, which preferentially develop into regulatory B cells, directly bound molecules released by the worm. No neighboring cells were necessary for these B cells to respond to the worm molecules. We could also identify a single worm protein, called IPSE/alpha-1, that can induce IL-10 production, both in B cells of mice and humans. We moreover found evidence that there are additional molecules which can also have this effect (**chapter 3**).

The induction of regulatory B cells by a chronic *S. mansoni* infection can thus also be achieved by a single worm molecule such as IPSE/alpha-1. This induction of regulatory B cells by isolated molecules is however less strong compared to the full infection, which suggests that there are several components working together in the case of an infection. To identify more signals and processes that contribute to the induction of regulatory B cells in an infected host, we compared which genes are expressed in the different B cell subsets from chronically *S. mansoni*-infected mice. We could identify several interesting signals and processes that seem more important for one of the B cell subsets than the other and might therefore play a role in the development of regulatory B cells. Amongst those were members of the type I interferon cytokine family, but also several elements of the innate immune system (**chapter 4**).

Type I interferons were thus suggested to be preferentially important for the activation of regulatory B cells in chronic *S. mansoni* infection. It had also been reported that different worms can trigger the production of these type I interferons, and that they are important in the activation of regulatory B cells in humans. We therefore further investigated whether type I interferons also provide signals for the induction of regulatory B cells in the context of *S. mansoni*. We found that type I interferons enhance regulatory B cell IL-10 production in response to *S. mansoni* molecules in a culture plate, but that they are not important in the body (**chapter 5**). Further research is therefore needed to identify the conditions that do lead to an optimal development and activation of regulatory B cells, and to better understand which role type I interferons play in parasitic worm infection.

The second part of this thesis focuses on the identification of *S. mansoni*-derived molecules that are protective in experimental models of allergic asthma. **Chapter 6** summarizes and discusses the scientific literature with respect to earlier findings for worm-induced protection from allergic asthma and the mechanisms of protection. In addition, studies are described that have identified protective worm molecules as well as their implications for the development of novel treatment strategies for allergic asthma.

Chronic *S. mansoni* infection had been shown to protect from allergic asthma in animal models, and infected humans are less likely to have allergies or asthma. We could show that isolated *S. mansoni* eggs, in the absence of infection, protect from experimental allergic asthma when administered to mice before they are exposed to allergenic substances for the first time. We could also reproduce the protective effect of eggs on allergic asthma in mice by a similar treatment with the worm-derived protein omega-1, for which no such role had been described before (**chapter 7**).

In conclusion, the work presented in this thesis shows that both the induction of regulatory B cells, as well as the protection from allergic asthma by a chronic worm infection can also be achieved by single molecules isolated from the worm. This work however also shows that immunological processes in response to a chronic worm infection are complex and often act in synergy. This thesis contributes to the understanding of how regulatory B cells are induced, and how molecules secreted by the parasite provide protection against allergic asthma. A deeper understanding of these fundamental immunological processes is necessary and will open up opportunities to develop new treatment options based on targeted interventions in immune processes.