1

General introduction

The prevalence of allergic diseases such as asthma, allergic rhinitis, and eczema and chronic inflammatory diseases such as type 1 diabetes, multiple sclerosis, and inflammatory bowel disease has increased dramatically in high-income countries in recent decades[1-9]. For example, in Swedish schoolchildren, the prevalence of asthma, allergic rhinitis, and eczema has doubled between 1979 and 1991[10]. The incidence of allergic and chronic inflammatory diseases started to increase in the 1950s, and is still rising for most of them[1]. In some lower-income countries, the prevalences also start to increase, but these diseases remain relatively uncommon[11]. Nowadays, an estimated 235 million people suffer from asthma, which encompasses 8% of all Americans, while 23% of adults in western Europe have allergic rhinitis[12-14]. In addition, more than 400,000 people in the United States of America (USA) and 2.5 million people around the world are thought to have multiple sclerosis[15]. These high numbers underscore the impact of allergic and chronic inflammatory diseases on the lives of many people, the society, and health care.

The Old Friends hypothesis states that the recent increase in inflammatory diseases in high-income countries is caused by immune dysregulation resulting from a lack of exposure to organisms with which humans have co-evolved, the Old Friends[8]. A vigorous immune response to these organisms would be needlessly damaging and, therefore, the immune system has evolved immune regulation[8]. However, this immune regulation would also result in bystander suppression of inflammation, such as against allergens, self-antigens, and gut content, and would therefore protect against allergic and chronic inflammatory disorders that could otherwise be provoked[8]. Public health measures and antibiotics use since the 1950s could have reduced or delayed exposure to the Old Friends and thereby resulted in the increased prevalences of allergic and inflammatory disoreders[8]. Indeed, changes have been observed in the composition of gut, skin and lung flora and in the presence of orofaecally transmitted chronic infections, helminths, environmental pseudocommensals, and ectoparasites in or on the human body[8]. Furthermore, the effects due to changed exposure to the Old Friends might have been aggravated by changes in modern lifestyle and the environment, such as obesity, vitamin D deficiency, and dioxins[8].

The reverse side of the coin is that in areas where inflammatory diseases are less prevalent due to possible immune regulation, vaccine responses could be compromised. For example, the protection against tuberculosis by the Bacillus Calmette–Guérin (BCG) vaccine varies from 0% to 80% and the response to this vaccine is stronger in the United Kingdom than in Malawi[16,17]. Likewise, vaccines against rotavirus diarrhoea, malaria, and yellow fever have provided lower protection in Africa as compared to Europe or the USA[18-20]. Therefore, further understanding of the immunological differences between populations would aid vaccine development efforts.

Despite large differences seen in disease prevalences or vaccine efficacy in different geographical areas, relatively few studies have investigated the underlying immunological mechanisms. There are few reports on differences in the immune system between populations, for example between individuals from high-income countries and those from lower-income

countries or rural versus urban areas within a country, where large environmental differences could influence immune responses[21-24].

Thesis outline

In this thesis, immunological differences between populations are investigated. A better understanding of these differences could aid in the development of population-specific vaccines and treatments against infectious, allergic, and chronic inflammatory diseases.

First, effects of environmental exposure on humoral immunity are studied. As glycosylation of antibodies is thought to modulate their effector functions, alterations in glycosylation could fine-tune the outcome of antibody responses to their specific antigens. In **Chapter 2**, the effect of three vaccines on immunoglobulin G (IgG) Fc N-glycosylation is studied in European adults as well as African children. In **Chapter 3**, IgG glycosylation is compared between populations with varied environmental exposure from different parts of the world. These chapters together provide information on the effect of a single antigenic challenge as well as composite life-long exposures on antibody glycosylation in diverse populations.

Subsequently, *ex vivo* cellular immune profiles and *in vitro* cellular immune responses are investigated. In **Chapter 4**, innate immune responses to a range of toll-like receptor (TLR) and non-TLR stimuli are compared between Europeans and semi-urban and rural Africans, while in **Chapter 5**, the adaptive $CD4^+$ T cell and B cell profiles of Europeans and urban as well as rural Africans are compared. In **Chapter 6**, both innate monocyte and adaptive $CD4^+$ T cell profiles in addition to *in vitro* immune response are compared between Europeans, urban and semi-urban Africans. By comparing rural and urban Africans next to Europeans, the effects of environmental differences can be assessed while minimising those due to genetic differences. Thus, these chapters together provide a picture of the immune system of Europeans and Africans under steady state, and their capacity to respond to *in vitro* stimulation.

The final chapters continue from there and compare whether *in vivo* immune responses are also different between Europeans and Africans. In **Chapter 7**, comprehensive immune profiles are determined first for Europeans and Africans, after which their *in vivo* response to controlled malaria infection is studied. In addition to controlled malaria infection, the response of γδ T cells and $CD4^+$ T cells to natural malaria infection is followed over time in Indonesia and reported in **Chapter 8**. Therefore, these chapters provide insight into the natural immune response against malaria infection. Finally in **Chapter 9**, the findings in the thesis are discussed succinctly.

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