Immunology Letters 162 (2014) 113–120

Contents lists available at ScienceDirect

Immunology Letters

journal homepage: www.elsevier.com/locate/immlet

Review

Inflammatory responses to infection: The Dutch contribution

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ARTICLE INFO

Article history:
Available online 18 October 2014

This paper is dedicated to Professor Joep Lange, a Dutch pioneer in AIDS research and a great protagonist of access to effective antiretroviral therapy for all. On July 17 this year, Joep died in the plane crash in Ukraine on his way to the AIDS conference in Australia.

Keywords:
Infection
Pathogen
Inflammation
Immune response
Dutch

ABSTRACT

At any given moment, our body is under attack by a large variety of pathogens, which aim to enter and use our body to propagate and disseminate. The extensive cellular and molecular complexity of our immune system enables us to efficiently eliminate invading pathogens or at least develop a condition in which propagation of the microorganism is reduced to a minimum. Yet, the evolutionary pressure on pathogens to circumvent our immune defense mechanisms is immense, which continuously leads to the development of novel pathogenic strains that challenge the health of mankind. Understanding this battle between pathogen and the immune system has been a fruitful area of immunological research over the last century and will continue to do so for many years.

In this review, which has been written on the occasion of the 50th anniversary of the Dutch Society for Immunology, we provide an overview of the major contributions that Dutch immunologists and infection biologists have made in the last decades on the inflammatory response to viral, bacterial, fungal or parasitic infections. We focus on those studies that have addressed both the host and the pathogen, as these are most interesting from an immunological point of view. Although it is not possible to completely cover this comprehensive research field, this review does provide an interesting overview of Dutch research on inflammatory responses to infection.

1. Introduction

Originally, the immune system of multicellular organisms evolved for the defence against microorganisms. During their evolution, vertebrates and especially mammals developed a very sophisticated immune system consisting of an innate and an adaptive arm. Despite this sophistication, pathogenic microorganisms may win the battle, in the worst case leading to death of the mammalian host.

The insight of scientists in the pathophysiology of infection and in host defence emerged slowly over the past centuries. Although the Dutch inventor of the microscope, Antoni van Leeuwenhoek, had discovered microbes around 1675, and the visionary scholar Girolamo Frascoro had postulated seminaria (small seeds or "germs") as causes of communicable diseases already in 1546, the microbial discoveries of Pasteur and Koch were needed to establish the microbial pathogenesis of infectious diseases. Dutch scientists, especially those of the "Delft school" (Beijerinck, Kluyver, Van Niel), delivered important contributions in the early days of microbiology, i.e. during the end of the 19th century and the first decades of the 20th century [1]. In fact, it was Martinus Beijerinck who introduced the term "virus" in 1898, for the filterable agent infecting tobacco plants, which he called 'contagium vivum fluidum' and which is now is known as tobacco mosaic virus [2].

Relevant discoveries in especially parasitology were made by scientists (Swellengrebel, Schüffner) in The Netherlands East Indies (Indonesia) in the first half of the twentieth century [3]. However, significant research dealing with the host immune response to infection, following the work of Ehrlich, Metchnikoff and von Behring, was not performed in The Netherlands. Vaccine development and antiserum production, "applied immunology", had started in 1919 in The Netherlands, coming to full bloom after 1953 under the leadership of Hans Cohen.

In this paper, which was written on the occasion of the 50th anniversary of the Dutch Society for Immunology, we describe the major research activities and accomplishments of research dealing with the immunology of infectious diseases in The Netherlands, during that era. Although separating this area of immunological research from other areas is artificial, we had to be rather strict in our selection, i.e., to be included in this overview, research had to

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http://dx.doi.org/10.1016/j.imlet.2014.10.007
0165-2478/

Table 1
Host/virus interaction.

Virus	Year	Findings	Reference
HIV	1988	Experimental induction of Early-type specific antibodies against HIV-1	[5]
	1992	Deletion of antigen-reactive T cells in HIV-1 infection is driven by aspecific T cell activation	[8]
	1995	HIV-1 specific CD8 T cells do not protect against the progression of HIV–infection to AIDS	[7]
	1996	Initial viral rebounds during HIV-1 suppression caused by treatment-induced CD4 T cell increase	[12]
	1996	CD4 T cell loss in HIV-1 infection is not due to proliferation-induced exhaustion	[4]
	1998	Extracellular granzymes A and B present in plasma and increases upon HIV-1 and EBV infection	[126]
	2000	Identification of DC-SIGN and molecular mechanism how HIV-1 transmission by DCs occurs	[13,127]
	2000	HIV-1 variants using coreceptor CXCR4 accelerate CD4 T cell loss by infecting naïve T cells	[6]
	2000	T-cell proliferation and deletion in HIV-1 is a consequence of generalized T cell activation	[9]
	2007	Langerhans cells are protected from HIV-1 infection by the C-type lectin receptor langerin	[14]
	2009	Sugar-specific signaling through DC-SIGN shapes immunity to viruses and bacteria	[15]
	2010	HIV-1 variants with long variable loops in envelope escape antibody neutralization	[10]
	2010	Cross-reactive neutralizing antibodies do not protect against disease progression in HIV-1	[11]
Influenza	1999	Polyclonal memory T cell populations to influenza provide protection against a range of viral variants	[16]
	2006	Innate immune response during Influenza A infection is associated with disease severity	[27]
	2008	Development of human antibodies with broadly neutralizing capacity against influenza	[22]
	2009	CD200-CD200R interactions attenuate T cell-mediated immune pathology upon influenza infection	[25]
	2009	Constitutive costimulation through CD27 impairs CD8 T cell memory to influenza	[24]
	2011	Discovery of functional intraepithelial CD8 T cells against influenza in human lung	[17]
	2011	Recall T cell responses peak within 1 week after the start of influenza	[18]
	2011	Costimulation through CD27 regulates T cell cross-reactivity against influenza variants	[19]
	2011	Development of human antibodies with broadly neutralizing capacity against influenza	[23]
	2012	CD200R ligation inhibits TLR7 signaling and IFN production, without affecting influenza clearance	[26]
	2013	Low pathogenic influenza strains induce NK cell responses, but high pathogenic strains do not	[20]
	2014	Nasal vaccination to influenza with bacterium-like particles induces TLR2-dependent immunity	[21]
CMV	1992/95	Virus-specific T cell responses in blood correlates with clinical responsiveness to CMV	[28,29]
	2003	Importance of CD4 T cells in primary response to human CMV	[30]
EBV	2003	EBV gp42 contributes to immune evasion by blocking TCR-MHCII interactions	[32]
	2007	Early EBV lytic cycle gene BNLF2a prevents CTL-mediated lysis by interfering with the TAP complex	[33]
	2007	EBV impairs protein synthesis in infected cells through BGLF5-induced mRNA degradation	[34]
	2012	CD27 deficiency is a combined immunodeficiency with persistent symptomatic EBV viremia	[31]
	2014	EBV attenuates TLR signaling through the deubiquitinase activity of BPLF1	[35]
HPV	1995	Eradication of HPV-induced tumors in mice by vaccination with a subdominant CTL epitope from HPV	[36]
	1995	Identification of immunogenic peptides from HPV16 E6 and E7 that can be used for vaccination	[37]
	1996	Evidence for natural immunity against HPV16 epitopes in patients with HPV16+ cervical lesions	[38]
	1999	Only cervical precursor lesions with a persistent HPV infection show progression to cancer	[39]
	2009	Vaccination with long peptides from HPV16 can induce remission of HPV-induced lesions	[40]
Other	1977	Cellular immune response to vaccinia virus in humans is associated with HLA	[41]
	1978	Measles virus can enter and be activated inside resting lymphocytes	[42]
	1988	Sensitivity to lymphomas by murine leukemia virus is determined by MHCII-regulated immunity	[128]
	1989	Successful immunotherapy with CD8 T cells directed against an epitope in an adenoviral protein	[129]
	2010	SARS in aged macaques shows exacerbated innate response; type I IFN as potential intervention	[43]
	2010–13	IFNγ-production upon LCMV infection dramatically alters hematopoiesis in bone marrow	[48–50]
	2012	Double-stranded RNA upon cellular infection with picornavirus is recognized by MDA5	[45]
	2013	Antibodies in camels to Middle East respiratory syndrome coronavirus indicate widespread infection	[44]
	2013	The deubiquitinase activity of PLP2 from arterivirus inhibits innate immune signaling	[47]
	2014	Enteroviruses repress transcription of IFN genes through cleavage of MDA5 and MAVS	[46]

deal with both host and pathogen for a paper to be included. To develop the lists of major contributions to immunological progress (depicted in Tables 1–4), we had several brainstorms, interviews, and performed searches in PubMed. This led to a long list of Dutch scientists that were felt to have significantly contributed to the understanding of the immunology of infection, thereby focussing on research that was also performed in The Netherlands. Our next step was to contact these people and ask them to provide us with no more than 3 of their most contributory publications. With this information, using the premises formulated above, we were able to construct the tables below. We chose not to go for a bibliometric approach for a number of reasons. First of all, the bibliometrics in this field appears to be flawed by rather arbitrary listing in one of the following fields: immunology, microbiology, infectious diseases, public health, and medicine. Secondly, the real impact of articles is often difficult to assess. A certain idea or concept may not be readily taken up, or even may be captured by others. Also the publication habits have profoundly changed over the past decades.

When we had gathered the articles that we wanted to include in this review, an important dilemma was how to order these contributions. We decided not to use an historical order, neither did we opt for investigators, groups or institutions, because mobility of investigators, contributions spanning many years, collaborations between institutions would lead to a distorted representation. So finally we decided to choose the order according to the major microorganism studied.

2. Viral infections

In Table 1, contributions to host and virus interactions are presented. Dutch scientists were highly active immediately after the emergence of AIDS. This was possible because of the infrastructure created by the public health epidemiologist Roel Coutinho and the virologist Jan van der Noordaa. They facilitated the work of Goudsmit, Miedema, Lange and Schuitemaker, as described in Table 1. The effects of antigenic variation, the non-protective antibody responses and the dynamics of the T cell compartment were described by these investigators [4–12]. Other important contributions have been made at the level of receptors that mediate HIV transmission to either dendritic cells (DCs) or T cells [13–15].

Table 2
Host/bacterium interaction.

Bacterium	Year	Findings	Reference
Staphylococcus	1979	Intracellular killing of bacteria by monocytes requires extracellular Igs and complement	[51]
	1983	Differential role of monocytes and granulocytes during course of Staphylococcus endocarditis	[52]
	1990	Bacterial iron contributes to oxidative killing of *S. aureus*	[53]
	1996	The complex clinical course of *S. aureus* bacteremia is not due to a relative lack of specific opsonins	[130]
	2005	Staphylococcal complement inhibitor decreases bacterial phagocytosis and killing by neutrophils	[55]
	2009	Staphylococcal SSL5 is immunomodulatory by targeting several stages of leukocyte extravasation	[56]
	2013	Staphylococcal toxin leukocidin targets C5a receptors, thereby regulating bacterial virulence	[57]
Neisseria	1992	The T cell repertoire against meningococcal OMP is more diverse than assumed	[65]
	1994	Fulminant meningococcal sepsis is associated with downregulated ex vivo cytokine production	[60]
	1997	The cytokine response in meningococcal sepsis soon turns into an anti-inflammatory repertoire	[61]
	1997	A genetically determined anti-inflammatory cytokine profile contributes to fatal meningococcal disease	[62]
	1998	Description of a *Neisseria meningitidis* mutant that can survive without lipopolysaccharide	[58]
	1999	Genetic predisposition to produce high PAI-1 levels impairs outcome of meningococcal sepsis	[63]
	2009	Natural mutant of *Neisseria meningitidis* with altered LPS form has low TLR4-activating capacity	[59]
	2010	Susceptibility to meningococcal disease depends on genetic variation in complement regulators	[64]
Mycobacterium	1976	Host response to *Mycobacterium leprae* is controlled by at least two HLA-linked genes	[66]
	1986	First identification of protein antigens from *M. leprae* that can activate specific CD4 T cells	[67]
	1993	Major antigenic epitopes from *M. leprae* are differentially expressed in leprosy lesions	[68]
	1997	Role of *M. leprae*-specific Th1 cells in driving tissue damage during reversal reactions in leprosy patients	[69]
	1998	IL-12R deficiency increases sensitivity to mycobacterial and *Salmonella* infections in humans	[70]
	2003	Mannose caps on glycolipid of *M. tuberculosis* targets enable binding to DC-SIGN	[71]
	2007	siRNA screening identifies AKT signaling network that controls intracellular bacterial growth	[72]
	2009	Antisense-mediated exon skipping can be used to correct the IL-12R gene defect in vitro	[131]
	2009	Sugar-specific signaling through DC-SIGN shapes immunity to viruses and bacteria	[15]
	2013	Lower induction of pro-inflammatory cytokines parallels evolutionary success of modern Beijing strain	[73]
Salmonella	1987	Genetic background determines the capacity of phagocytes to kill *Salmonella*	[74]
	1998	IL-12R deficiency increases sensitivity to mycobacterial and *Salmonella* infections in humans	[70]
	2009	BCR-mediated internalization of *Salmonella* by B cells efficiently induces humoral immunity	[75]
	2012	*Salmonella*-specific B cells can act as a survival niche and a reservoir for reinfection	[76]
Bordetella	2001	Clearance of *Bordetella pertussis* is driven by Fcgamma receptors rather than by CR3	[77]
	2003	Antibodies to pertactin are crucial to phagocytosis of *Bordetella pertussis*	[77]
Helicobacter	1996	Molecular mimicry between Lewis blood group antigens and LPS of *H. pylori*	[79]
	2004	Mutation in fucosyltransferase of *H. pylori* alters Th1/Th2 balance through DC-SIGN	[80]
	2009	Sugar-specific signaling through DC-SIGN shapes immunity to viruses and bacteria	[15]
Gut	1974	Intestinal microflora has a strong impact on allogeneic lymphocyte responses in GVHD	[81]
flora	1977/88	Resident intestinal microflora plays a role in the occurrence of GvHD	[82,83]
	2001	Immune status of mother and pup controls bacterial colonization in neonates	[84]
	2010	Microbiota composition in the gut is highly dependent on presence of enteric defensins	[85]
Sepsis/endotoxins	1988	Circulating endotoxins as good predictors of septicaemia in patients with bacterial infection	[86]
	1988	Low dose IL-1 enhances survival of *Pseudomonas* infection in neutropenic mice	[87]
	1989	IL-6 levels are increased in septic patients and correlate with disease severity	[88]
	1990	Single injection of recombinant TNFα is sufficient to cause activation of the coagulation system	[89]
	1990	Thorough analysis of innate immune responses upon experimental endotoxemia in humans	[93]
	1993	BPI is expressed on the surface of the granulocyte	[54]
	1996	Reconstituted high-density lipoprotein has anti-inflammatory effects during endotoxemia	[95]
	1996	Epinephrine inhibits TNFα release and enhances IL-10 production upon endotoxin challenge	[94]
	1998	High IL-10/TNF ratio is associated with mortality in community acquired infection	[90]
	2007	TLR2 rather than TLR4 plays important role in Burkholderia-induced sepsis	[91]
	2012	IFN-γ partially reverses endotoxin-induced immunoparalysis in vivo in humans	[96]
	2012	Endotoxin challenge in humans induces a subset of neutrophils that inhibit T cell responses	[97]
	2012	Extracellular granzyme K enhances endotoxin-induced cytokine responses by human monocytes	[92]
	2014	Voluntary activation of the sympathetic nervous system can attenuate response to endotoxin	[98]
Other	1979	Epidemic with typhoid and yellow fever has induced natural selection of certain HLA types	[99]
	2006	Fc receptor polymorphisms influence the response to pneumococcal polysaccharides	[101]
	2007	TLR4 polymorphisms were under evolutionary pressure during human migration	[100]
	2007	Enzymatic cleavage of CXCR1 on lung neutrophils in CF patients reduces bacterial killing	[132]
	2011	Avian TLR15 is a sensor for secreted microbial proteases	[133]

Table 3
Host/fungus interaction.

Fungus	Year	Findings	Reference
Candida	1988	Granulocytes, not monocytes or exudate macrophages, are important in resistance against *C. albicans*	[102]
	2003	DC-SIGN enables DCs to bind and internalize *C. albicans*	[105]
	2006	Immune recognition of *C. albicans* is dependent on various pattern recognition receptors	[106]
	2009	CD37 regulates the immune response against *C. albicans* by inhibiting IgA responses	[107]
	2011	Role of STAT1 and Th17 in autosomal dominant chronic mucocutaneous candidiasis	[103]
	2012	BCG protect against *Candida* infection by epigenetic reprogramming of monocytes	[108]
	2014	Both ROS-dependent and ROS-independent killing mechanism of *C. albicans* by neutrophils	[104]
Cryptococcus	2004	VEGF produced in cryptococcal meningitis may lead to blood–brain barrier disruption	[109]

Table 4
Host/parasite interaction.

Parasite	Year	Findings	Reference
Trypanosomes	1980/82	Antigenic variation of variant surface glycoproteins of trypanosomes revealed	[110,111]
	1998	Trypanosomes prevent recognition by host species-specific usage of transferrin receptor isoforms	[112]
Plasmodium	1983	*P. berghei* sporozoites are harbored by Kupffer cells and then rapidly escape into hepatocytes	[114]
	1985	Identification of *P. falciparum* vaccination target proteins involved in human–mosquito transmission	[113]
	1995/96	Development of genetically modified malaria parasites	[115,116]
	2005	Protective immunity to malaria can be induced with genetically attenuated sporozites	[117]
	2009/13	Successful immunization strategies that can protect against malaria	[118,119]
Schistosoma and other worms	1998	Schistosomiasis leads to hyporesponsive T cells	[121]
	2000	Schistosoma-induced IL-10 production correlates with lower occurrence of atopy in children	[122]
	2010	Immune responses to BCG and *P. falciparum* are suppressed by worm-induced regulatory T cells	[120]
	2012	Schistosoma-derived Omega-1 induces Th2-mediated responses via dendritic cells	[123]
Other	1976	Intestinal mast cell response following *Trichinella spiralis* infection is dependent on T cells	[124]
	1994	Adaptive immune responses to *Leishmania infantum* correlate with disease progression in dogs	[125]

Another virus that has been studied by several Dutch research groups is Influenza A. This work ranges from the cellular and molecular mechanisms that drive protective anti-viral immunity [16–21], to the development of human antibodies with broadly neutralizing capacity against the virus [22,23]. Investigation into the cellular anti-viral response encompassed the polyclonality of the responding T cell pool, the role of T cell co-stimulation and the formation of memory T cells, but also the involvement of innate immune cells their contribution to pathology [16,18–20,24]. Moreover, it has been shown that the inhibitory receptor CD200R plays an important role in diminishing immune pathology during influenza [25,26]. Many approaches to study the immune response to influenza relied on the mouse as experimental model [16,19,21,24–26], but several groups have also been able to perform their analysis on human cells and tissues [17,18,27].

Analysis of anti-viral responses directly in humans is of great value and has also been done for latent viruses such as cytomegalovirus (CMV) and Epstein–Barr virus (EBV) by several Dutch groups, which has revealed the great importance of our adaptive immune system to keep these infections in check [28–31]. Identification of several specific strategies of EBV has provided insight into the molecular details on how this virus is able to evade the immune system and establish latency [32–35]. Moreover, important contributions have also been made at the level of persistent infection with human papillomavirus (HPV), which is key for the development of cervical cancer: human T cell epitopes from HPV have been identified and shown to be effective in peptide vaccination to HPV [36–38], which can subsequently induce remission of HPV-induced cervical lesions in patients [39,40]. This has resulted in the decision of the Dutch government in 2010 to add HPV-vaccination for 12-year-old girls to the existing national immunization program.

Other Dutch contributions to anti-viral immunity have been made with vaccinia virus [41], measles [42], SARS [43] and MERS [44], but also at the level of intracellular recognition of viruses [45], viral dysregulation of innate sensing/interferon responses [46,47] and how interferon-gamma production upon viral infection regulates hematopoiesis [48–50].

3. Bacterial infections

The defence of the host against bacterial pathogens has been an intensive area of investigations in The Netherlands (Table 2). At the side of the host, the function of phagocytic cells (granulocytes and mononuclear phagocytes) was investigated in different groups since the 1970s. The relevance of oxidative and non-oxidative bactericidal mechanisms, the importance of monocytes and macrophages, the activation of phagocytic cells were topics in many papers [51–54]. Since the 1980s, the role of cytokines in the inflammatory response toward bacterial pathogens also became an important topic. Looking from the site of the bacterium, *Staphylococcus aureus* and especially its serious virulence and immune evasion have been intensively studied [55–57].

Because of the high prevalence of serious meningococcal infection (especially serotype B) in The Netherlands at the end of the last century, several groups performed research to elucidate the interaction between this pathogen and the host. These studies yielded important insights in the role of the Neisserial endotoxin [58,59], the overwhelming inflammatory response and its subsequent downregulation (nowadays indicated as 'immune paralysis') [60,61], the genetic background of susceptibility [62–64] and in the adaptive immune response, relevant for vaccine development [65].

Much work has been done on the interaction between mycobacteria (*Mycobacterium leprae* and *Mycobacterium tuberculosis*) and the immune system [15,66–73]. The role of HLA and T-cell recognition in leprosy [66,67], the interaction of *M. tuberculosis* with DC-SIGN [15,71] and the role of cytokines and their receptors in susceptibility [70] are among the major findings. Other bacteria that have been the subject of Dutch research in immunology are *Salmonella* spp. [70,74–76], *Bordetella pertussis* [77,78] and *Helicobacter pylori* [15,79,80].

Pioneering work on the gastrointestinal flora and the induction of graft versus host disease was done by Van Bekkum and Van der Waaij in the 1970s and 1980s [81–83]. Later on, it was shown by the Bos group that bacterial colonization in neonates is controlled by the immune status of both mother and pup [84], and that enteric defensins also play a critical role in this process [85].

Parallel to the work on meningococcal sepsis, a large amount of studies was published on bacterial sepsis, the role of endotoxin and of potential interventions [86–92]. Important insights in the pathophysiology of sepsis were obtained in the experimental endotoxemia in human volunteers [93–98].

With regard to genetic susceptibility to infection, an early elegant study was done by De Vries and Van Rood; they convincingly showed that severe infections in humans causes natural selection of certain HLA types [99]. Nearly 30 years later similar effects were shown for TLR4 polymorphisms during human migration by Netea et al. [100]. Genetic susceptibility to infection was also studied for specific pathogens such as meningococci [62–64], pneumococci [101], mycobacteria [66,70] and *Salmonella* species [70,74].

4. Fungal infections

Studies on host defence against the major fungal pathogen *Candida albicans* started in the 1980s, in an era when disseminated infections with this opportunistic pathogen became more

prevalent in The Netherlands. These invasive infections were especially prominent in patients with neutropenia and those with neutrophil dysfunction disorders, and hence it was obvious to initiate studies on the role of phagocytic cells, i.e., granulocytes and monocytes [102].

An intriguing group of patients with undue susceptibility to *Candida* species, as well as to dermatophytes, are patients with chronic mucocutaneous candidiasis. The elucidation of the defect in these patients, specifically with the autosomal dominant form, would take until 2011, with the discovery that mutations of the STAT1 gene are responsible for a large proportion of these patients [103]. The defective subsequent production of interferons, IL-17, IL-23, leading to insufficient neutrophil activation and defensin production are considered to lead to the susceptibility to the fungal pathogens. In depth analysis of the fungicidal capacity of human neutrophils revealed that these cells can use two distinct and independent phagolysosomal mechanisms to kill *C. albicans*, being either reactive oxygen species-dependent when mediated by Fcγ receptors or reactive-oxygen species independent when mediated through complement receptor 3 and CARD-9 [104]. A thoroughly studied topic is that of recognition of *Candida* species by host cells. A series of molecular patterns on the surface of the fungus was identified as ligands for an array of pattern-recognition receptors [105,106]. On the other hand, the tetraspanin CD37 was found to inhibit IgA responses to *Candida* and thereby able to regulate the anti-fungal immune response [107]. In 2012, a new paradigm, 'trained immunity' was put forward by Netea's group, based on the observation that beta-glucan derived from *Candida* (and muramyl dipeptide from BCG) is able to enhance the innate immune effector function through epigenetic reprogramming of monocytes and macrophages [108].

The immunity to other fungal pathogens, *Cryptococcus neoformans* and *Aspergillus* species has also been studied. Here we mention the effect of *C. neoformans* on the production in the cerebrospinal fluid of VEGF, which is thought to be important in the disruption of the blood–brain barrier [109].

5. Parasitic infections

Seminal studies on the interaction between the host and *Trypanosoma bruzei* were performed by Borst and his group, demonstrating for the first time the incredible antigenic versatility of this parasite [110–112]. The parasite genome contains some 1000 genes encoding the variant surface glycoproteins, rendering vaccine development a futile undertaking.

Most of the work on parasites in Dutch immunology concerns malaria parasites. Meuwissen's group was the first to show the sequential appearance of antigens on the sexual stages of *Plasmodium falciparum*, the cause of tropical malaria [113]. This work formed the basis for development of transmission blocking vaccines. Another seminal study at that time dealt with the early liver form of the plasmodia [114]. Other Dutch research on malaria dealt with the technology to genetically modify and attenuate malaria parasites, in order to use these for immunization [115–117]. Another major advance in malaria research was obtained in the experimental malaria studies in human volunteers. Using this set up, pre-erythrocytic immunity was obtained by inoculating the volunteers with live *P. falciparum* sporozoites under chloroquine treatment, and the investigators were able to demonstrate long-lasting protection against a malaria challenge [118,119].

Intestinal helminth infestations, which are endemic in many non-western societies, appear to affect on the immune system of the host. Yazdanbakhsh and her group have performed many studies to assess these immunomodulatory effects in more detail. They demonstrated that regulatory T cells induced by these worms suppress the T cell response to plasmodia-parasitised erythrocytes and to BCG [120]. This work builds on earlier work, in which T-cell hyporeponsiveness induced by schistosoma infection was shown [121]. Induction of IL-10 by the schistosomes appeared to be an important effector mechanism [122]. The major schistosoma egg antigen Omega-1 was shown to induce Th2 polarization through ligation of the mannose receptor on dendritic cells [123].

Seminal work by Ruitenberg revealed that the increase of intestinal mast cells observed during the intestinal phase of infection with the nematode *Trichinella spiralis* is highly dependent on T cells, as it does not occur in athymic (nude) mice [124]. Interestingly, parasite infections were found to have even long-lasting effects on the immune system, as dogs infected with leishmania 3 years later greatly differed in the immune response according to their disease manifestations: asymptomatic dogs had a strong cellular immune response (with high IL-2 and TNFα production) while symptomatic dogs exhibited a mere antibody response [125].

6. Conclusions

In the present review we have attempted to cover nearly 50 years of Dutch immunological studies in the area of infectious diseases. Although we have tried to be complete, we are pretty sure that we have overlooked some important contributions. Moreover, because of the nature of this review, some topics and teams of scientists will have been more highlighted than others. For this we apologize. It is clear from the review that the scientists in The Netherlands that were and are active in this area have produced articles that had and still have quite an impact on the way we view host and pathogen interaction nowadays. It is interesting to see that – although there are areas with quite a large number of contributions (such as those on immunity to HIV, influenza virus, *S. aureus*, sepsis, endotoxin and malaria), there are important contributions dealing with many other infectious agents. It is also clear that the field is more active than ever before, and that we will see great future Dutch scientific contributions in this fascinating area.

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