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Review

Inflammatory responses to infection: The Dutch contribution

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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.

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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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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].