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99th Dahlem Conference on Infection, Inflammation and Chronic Inflammatory Disorders: Lifestyle changes affecting the host–environment interface

Introduction to and Summary of the 99th Dahlem Conference held in Berlin, June 10–13 2009

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Summary

In industrialized nations and high-income regions of the world, the decline of infectious diseases is paralleled by an increase in allergic, autoimmune and chronic inflammatory diseases (AACID). Changes in lifestyle in westernized societies, which impact individually and collectively on intestinal microbiota, may – at least in part – account for the AACID pandemic. Many disease genes that contribute to AACID encode pattern recognition and signalling molecules in barrier-associated cells. Interactions between gene products and environmental factors depend highly upon the host's state of maturation, the composition of the skin and gut microflora, and exposure to pollutants, antibiotics and nutrients. Inflammatory stress responses, if regulated appropriately, ensure immunity, health and relative longevity; when they are dysregulated, they can no longer be terminated appropriately and thus precipitate AACID. The 99th Dahlem Conference brought together experts of various disciplines (genetics, evolution biology, molecular biology, structural biology, cell biology, immunology, microbiology, nutrition science, epidemiology and clinical medicine) to discuss the multi-faceted relationships between infection, immunity and inflammation in barrier organs and the development of AACID. In *Clinical and Experimental Immunology* we are presenting a compilation of background papers that formed the basis of discussions. Controversial viewpoints and gaps in current knowledge were examined and new concepts for prevention and treatment of CID were formulated.

Keywords: allergy, autoimmunity, infection, inflammation, microbiome

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Introduction

Controlled inflammation in mucosa and skin is a normal feature of barrier maintenance to safeguard homeostasis against noxious attacks. Destructive inflammation evolves frequently from these processes. For example, in infection-induced inflammation, pathogenicity factors of microbial agents interact with receptors on host cells and induce damage as well as tissue repair.

Destruction and restoration in inflammatory diseases are the result of a complex interplay of host gene expression, structural features of environmental triggers and regulatory feedback loops. In human chronic–inflammatory disorders (e.g. inflammatory bowel disease, atopic eczema, asthma, psoriasis, type 1 diabetes, multiple sclerosis, vasculitis), polygenetic susceptibility is one of the prerequisites for disturbed interactions with unknown external agents [1,2]. The epidemiology of a changing environment resulting from the lifestyle of industrialized western societies can explain, at least in part, rising incidences of many of these diseases. In fact, chronic inflammatory, allergic, autoimmune and malignant diseases have largely replaced infectious diseases in

industrialized countries, and are rising in higher-income regions even in developing and newly industrialized countries [3].

Increasing evidence suggests close interactions between infectious diseases and chronic inflammation. Infectious agents contribute directly or indirectly to chronic inflammation and cancer [4–6]. These include *Helicobacter pylori* for stomach cancer, hepatitis B and C for liver cancer, group A streptococci for rheumatic fever and human papillomavirus (HPV) for cervical cancer, to name a few. Moreover, the 'hygiene hypothesis' claims a reciprocal relationship between infection and increasing incidences of allergy and autoimmune diseases [7,8]. Recent insights provide a more complex scenario, where microbial pathogens and commensals synergize to drive or antagonize allergic, autoimmune and inflammatory diseases. Thus, numerous infectious agents act as co-factors for various chronic inflammatory diseases, the normal gut flora of humans apparently has an influence on body weight and overall immune defences and both pathogens and normal flora influence predisposition for allergy and autoimmune diseases. The failure to prime and differentiate regulatory T cells adequately is one likely basis for various chronic diseases (possibly including depressive and neurodegenerative disorders) [9,10].

The Dahlem Workshops: a think-tank setting to address gaps in knowledge

The interkingdom cross-talk between microbes and the human host, beyond infectious diseases, was at the center of the 99th Dahlem Conference (Box 1) on Inflammation and Infection. Its aim was to elucidate common and divergent pathways of infectious diseases and chronic inflammatory diseases with a focus on the interface between the human host and its environment. Therefore, the Dahlem Conference addressed issues of barrier function and their modulation by infection, nutrition, hygiene and co-evolving or co-existing autoimmune allergic and inflammatory disorders. World-renowned experts from different areas including molecular genetics, population epidemiology, structural biology, cell biology, immunology, nutrition sciences and animal research as well as clinical medicine convened to discuss the following questions that necessitated a highly interdisciplinary discourse:

- What is the relationship between the immune response to infectious and environmental agents and the development of allergic and chronic inflammatory diseases?
- Is there a causal link between the decline in infectious diseases and the emergence of allergic, autoimmune and chronic inflammatory disorders?
- What are the common molecular pathways in initiating, maintaining and terminating protective and pathological responses to environmental insults?

Box 1: the Dahlem Konferenzen

In 1974, the Stifterverband für die Deutsche Wissenschaft [the Donors Association for the Promotion of Sciences and Humanities, a foundation created in 1921, in Berlin, and supported by German trade and industry to fund basic research in the sciences] in co-operation with the Deutsche Forschungsgemeinschaft [German Science Foundation] founded the Dahlem Konferenzen (Dahlem Conferences). They were created to promote an interdisciplinary exchange of scientific ideas as well as to stimulate cooperation in research among international scientists. Dahlem Konferenzen proved to be an invaluable tool for communication in science and so, to secure a long-term perspective, were integrated into the Freie Universität Berlin in 1990.

Dahlem Konferenzen has created a special type of forum for communication, now recognized internationally as the Dahlem Workshop Model. These workshops provide a framework in which coherent discussions between different disciplines take place around a topic of high-priority interest to a broad spectrum of research areas. At a workshop, scientists pose questions and solicit alternative opinions on contentious issues from colleagues in related fields. The overall goal of a workshop is not necessarily to reach a consensus, but rather to identify gaps in knowledge, to define controversial issues and to set priorities for future research. This philosophy is implemented at every stage of a Dahlem Conference: from the selection of the theme to its breakdown in the discussion groups, from the writing of the background papers to the composition of the group reports.

Conference topics are proposed by leading scientists and are approved by a scientific board, which is advised by qualified referees. Once a topic has been approved, a Programme Advisory Committee of scientists meets approximately one year in advance to delineate the scientific parameters of the meeting, select participants and assign them specific tasks. Participants are invited on the basis of their scientific standing only.

Every conference is organized around four key questions, each of which is addressed by a discussion group, i.e. Workshop, of approximately 10 participants. Lectures or formal presentations are taboo at Dahlem workshops. Instead, concentrated discussion – within a group and between groups – is the means by which maximum communication is achieved. To facilitate this discussion, participants prepare the workshop theme in advance through the 'background papers', the themes and authors of which are chosen by the Programme Advisory Committee. These papers review specifically a particular aspect of the group's discussion topic as well as function as a springboard to the group discussion, by introducing controversies or unresolved problem areas.

At the beginning of a Dahlem Conference week, each workshop sets its own agenda to cover the discussion topic. Cross-fertilization between groups is both stressed and encouraged. By the end of the week, each workshop has collectively prepared a report reflecting the ideas, opinions and contentious issues of the group as well as identifying directions for future research andproblem areas in need of further resolution.

- Can information gained in infection research be exploited to modulate chronic inflammation, allergies or autoimmunity, e.g. by vaccination or immunomodulation?
- How can inflammation medicine profit from evolution biology, plant immunology, host and microbe genetics, nutrition and immunology?
- To what extent are chronic inflammatory diseases the result of changes at the epigenetic level or of environmental factors, such as the intestinal microbiome or toxic pollutants, and can intervention by 'molecular nutrition' help correct this dysregulation?
- How does the concept of Darwinian medicine shed light on the interplay between disease susceptibility genes, decrease in infectious diseases and increase in inflammatory disorders in western societies?

This Dahlem Conference comprised four workshops, each with a different focus:

- Immunoregulatory consequences of microbial encounter;
- Molecular evolution of host–environment interfaces;
- Nutrition and microbiome as determinants of chronic inflammation;
- Epidemiology of autoimmune diseases and infectious diseases.

Individual meetings of the workshops were followed by joint sessions of two or more working groups discussing points of intersection and mutual agendas.

There were few, and only very short, presentations of original data; rather, the Dahlem Conference format encourages heated, but disciplined and engaged, debates on controversies and unresolved issues among leaders of specific research areas.

The Dahlem Workshop Model is based on background papers (provocative mini-reviews and opinion statements) prepared in advance and discussed in the atmosphere of a think-tank workshop by expert groups and plenary sessions of the entire panel. Participants of the 99th Dahlem Conference on 'Infection, Inflammation and Chronic Inflammatory Disorders' were (organizers, session conveners and rapporteurs are underlined): Frederick M. Ausubel, Jean-Francois Bach, Yasmine Belkaid, Bruce Beutler, John Bienenstock, Anita van den Biggelaar, Fredrik Bäckhed, Thomas Bosch, Lucienne Chatenoud, Robert Coffmann, Stephen M. Collins, Max D. Cooper, Stefan Ehlers, Paul Ewald, Alan Ezekowitz, Matthias von Herrath, Jules Hoffman, Patrick Holt, Jean-Luc Imler, Christopher Karp, Dennis L. Kaspar, Stefan H. E. Kaufmann, Rick Maizels, Paolo Matricardi, Samuel Miller, Stephen D. Miller, Lorenzo Moretta, Erika von Mutius, Liam O'Mahoney, Thomas Platts-Mills, Eyal Raz, Graham Rook, Paul Schulze-Lefert, Fergus Shanahan, Alan Sher, Ulrich Steinhoff and Dale T. Umetsu (see Fig. 1). All background papers containing additional references are presented here in *Clinical and Experimental Immunology* and provide an excellent overview of current research in this rapidly developing field [7,11–28].

Future areas of research

The Dahlem Conference did not restrict itself to the state of the art; rather, it developed new perspectives and formulated open questions for cross-disciplinary research to come (summarized in [29]). For example, the following gaps in knowledge were identified:

- What is the degree of plasticity of immune homeostasis among individuals and at different stages of life? How critical is the microbial environment in constraining or driving inter- and intraindividual variability in immune homeostasis? Are there critical stimulation thresholds?
- What are the molecular signals arising from the microbial environment that drive immunoregulatory responses? Do diverse classes of organisms share common patterns of molecules, signals and pathways?
- Which mechanisms underlie tissue specificity of immunoregulatory responses?
- What is the role of diversity of the microbial environment – both at a distinct point in time, and dynamically over time – in driving robust immunoregulation?
- Do polymorphisms in immune-related genes, which are linked with susceptibility to allergic autoimmune and inflammatory diseases, operate in this context through an altered host–microbe cross-talk?
- What are the mechanisms by which the dynamics of colonization after birth regulate immune maturation?
- How does maternal microbial exposure influence the developing immune system, pre- and postnatally?
- What is the relative importance of bona fide pathogens *versus* commensals, or pseudo-commensals, in instructing a robust counter-regulatory environment?
- Do pathogen-driven alterations in the commensal flora alter the immunoregulatory environment?
- Is the focus on microbial instruction of immune counter-regulation too narrow? Are inefficient immune activation and insufficient immune-mediated repair processes as important as inefficient counter-regulatory responses in driving CID?

The 99th Dahlem Conference emphasized that open-minded communication between diverse disciplines can not only uncover knowledge gaps, but also novel strategies to bridge them: after all, elucidation of the interkingdom cross-talk requires full use of our interdisciplinary capacities. In future epidemiological studies, for example, the following issues should be addressed:

- To which microbes, including helminths and ectoparasites, have subjects been exposed, and for how long?
- Are viable microbes (pathogens, symbionts, commensals) needed or do non-viable microbial components suffice?

Fig. 1. Photograph of all participants.

Are unique exposures or a diversity of different microbial exposures important?
- At what time in relation to the resulting disease process does exposure occur?
- What is the impact of the route and dose of exposure (e.g. inhalation, skin contact or ingestion)?

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