

Summaries G.A.W. Rook (ed.): The Hygiene Hypothesis and Darwinian Medicine

Summary

Graham A.W. Rook

Introduction: The changing microbial environment, Darwinian medicine and the Hygiene Hypothesis

Abstract

Man has undergone rapid cultural and technological evolution, with little simultaneous genetic evolution. Thus our physiology is adapted to the microbial exposures that prevailed in the hunter-gatherer environment, rather than to the clean living conditions of the rich industrialised countries. There is increasing evidence that lack of exposure to organisms that were part of mammalian evolutionary history is leading to disordered regulation of the immune system, and hence to increases in several chronic inflammatory disorders. The concept began with the allergic disorders, but there are now good reasons for extending it to autoimmunity, inflammatory bowel disease, neuroinflammatory disorders, atherosclerosis, depression associated with raised inflammatory cytokines, and some cancers. We discuss these possibilities in the context of Darwinian medicine. This approach enables one to identify some of the organisms that are important for the 'hygiene' or 'old friends' hypothesis, and to point to their potential exploitation in novel prophylactics and treatments, with applications in several branches of medicine.

Keywords: Darwin, evolution, evolved dependence, hunter-gatherer, regulatory T cells, helminths, mycobacteria, probiotics, Old Friends Hypothesis, interleukin-10, transforming growth factor β , allergy, autoimmunity, inflammatory bowel disease

Summary

George J. Armelagos

The paleolithic disease-scape, the hygiene hypothesis, and the second epidemiological transition

The hygiene hypothesis argues that in developed nations the lack of childhood exposure to infectious pathogens, parasites, and symbiotic microorganisms increases susceptibility to allergy and other chronic diseases in adulthood. A modified hygiene hypothesis, ('the old friends hypothesis' proposed by G. A. Rook) excludes childhood diseases as a requisite factor and focuses on organisms such as lactobacilli, a variety of saprophytic mycobacteria and helminthic parasites that are tolerated by the immune system and are absent from the pathogen load of developed nations. The exposure to these ubiquitous agents is postulated to help in the development of the T regulatory response that when absent in industrialized nations results later in the manifestation of allergies and an array of autoimmune diseases such as inflammatory bowel disease, multiple sclerosis, and Type 1 diabetes. To evaluate this hypothesis, I will examine the pattern of human diseases using a model of epidemiological transition modified from A. R. Omran's original formulation. The epidemiological transition provides a means of understanding the changing relationship between humans, pathogens and other disease insults from the Paleolithic period to the present. The adaptation of hominid populations in the Paleolithic created a disease ecology that minimized the impact of infectious disease but exposed the foragers to many saprophytic mycobacteria in the soil and

decaying plant matter. The shift to agriculture about 10,000 years ago heralded the first epidemiological transition characterized by the continued exposure to helminths and saprophytic environmental organisms, plus the emergence of additional infectious and nutritional diseases that continue to the present. The acceleration of urbanization and social inequality increases the spread of infectious disease. Within the last Century, some populations have undergone the second epidemiological transition in which public health measures, improved nutrition and medicine resulted in declines in infectious disease and a rise in non-infectious, chronic and degenerative diseases. This phase with the control of infectious disease and the development of a sanitized water supply and sewer system has played a role in the modified hygiene or 'old friends' hypothesis. It is a period in which 'cleanliness' removes us from contact with 'dirt'.

Summary

Rick M. Maizels and Ursula Wiedermann

Immunoregulation by microbes and parasites in the control of allergy and autoimmunity

Key changes in our microbial environment, encompassing mycobacteria, helminth worms and commensal microflora, may each have had a major impact on the development and reactivity of our immune system not only to infections, but also in the context of harmless antigens in autoimmunity and allergy. We discuss here recent advances in understanding host-microbe and host-parasite interactions, and their impact on the balance between immunoregulation and immunopathology in the mammalian immune system.

Keywords: allergy, autoimmunity, commensal microbiota, dendritic cell, helminth, hygiene hypothesis, mycobacteria, regulatory T cell, toll-like receptor

Summary

Dale T. Umetsu and Rosemarie H. DeKruyff

Hepatitis A virus, TIM-1 and allergy

In 1989, Strachan first proposed the hygiene hypothesis to explain the rapid increase in the prevalence of allergy and asthma. While the significant rise in the prevalence of asthma and allergy remains unexplained, epidemiological data suggest that infection with the Hepatitis A virus (HAV) might protect against asthma and allergy, and genetic studies identifying the HAV receptor, TIM-1, as an important atopy susceptibility gene, support this idea. In this chapter, we review the genetics and immunobiology of TIM-1 and TIM gene family members, and the possibility that HAV and TIM-1 may regulate the development of asthma and allergy.

Keywords: hepatitis A virus (HAV), TIM-1, atopy, allergy, asthma, food allergy, T cell, costimulation, Hygiene Hypothesis

Summary

Fergus Shanahan

Linking lifestyle with microbiota and risk of chronic inflammatory disorders

The inflammatory bowel diseases, Crohn's disease and ulcerative colitis, are among several immune-mediated disorders that consistently increase in incidence and prevalence when a society undergoes transition from 'developing' to 'developed' status. The impact of a changing lifestyle and environment associated with modernisation is greatest during early life. The mechanism may involve an alteration in composition or metabolic activity of the commensal microbiota colonising the host during early life. Since the commensal microbiota influences immunologic maturation and shapes the function of the developing immune system, disturbances in microbial biodiversity may contribute to individual variations in immunologic behaviour during and after childhood. Thus, an environmental influence on the commensal microbiota may underpin much of the changing epidemiology common to several immune-mediated chronic inflammatory disorders.

Keywords: mucosal immune system, microbiota, inflammatory bowel disease, Crohn's disease, ulcerative colitis, environment, lifestyle.

Summary

David R. Whitlock and Martin Feelisch

Soil bacteria, nitrite and the skin

Little is known about the composition of the skin microbiome and its potential significance for health and disease in the context of the 'hygiene hypothesis'. We here propose that mammals evolved with a dermal microflora that contributed to the regulation of body physiology by providing nitrite from commensal ammonia-oxidising bacteria in response to ammonia released during sweating. We further hypothesise that modern skin hygiene practices have led to a gradual loss of these bacteria from our skin. Together with other lifestyle-related changes associated with an insufficient bodily supply with nitrite and depletion of other nitric oxide(NO)-related species, a condition we here define as 'nitropenia', this has led to a perturbation of cellular redox signalling which manifests as dysregulated immunity and generalised inflammation. If proven correct, this scenario would provide an additional evolutionary rationale and a mechanistic basis for the simultaneous rises in prevalence of a number of seemingly unrelated chronic illnesses over the last 3–4 decades.

Keywords: nitric oxide, nitrite, redox signaling, inflammation, allergy, hygiene hypothesis, ammonia-oxidizing bacteria, T-cells, nitrification, nitropenia

Summary

Paolo M. Matricardi and Eckard Hamelmann

The hygiene hypothesis and allergic disorders

Allergic diseases are more frequent in the general population than other immune-mediated disorders, such as autoimmune diseases or immunodeficiencies. Therefore, epidemiological studies investigating the hygiene hypothesis in relation to allergic diseases have been performed much more frequently than those investigating the hygiene hypothesis in relation

to Crohn's disease, multiple sclerosis, rheumatoid arthritis or other diseases related to dysregulation of the immune system. More than one thousand papers have been written on this subject and it is not possible to condense them in a few pages. In this chapter, we summarise the most important pathways followed by the research on the hygiene hypothesis applied to allergic disorders, i.e., the allergy protective role of foodborne and orofaecal infections, starting from Strachan's initial observations and concluding with the most recent intervention studies.

Keywords: allergic diseases, allergic immune response, atopy, asthma, allergic rhinitis, hay fever, atopic dermatitis, food allergy, prevention, hygiene hypothesis, farm effect, probiotic, gut flora

Summary

Jorge Correale

Multiple sclerosis

Multiple sclerosis (MS) is an inflammatory demyelinating disease of the Central Nervous System (CNS). Although its etiology remains unknown, several lines of evidence support autoimmunity as playing a major role in the development of the disease. MS incidence has significantly increased during the second half of the 20th Century. This has been attributed to improved sanitation and reduced exposure to infection. The hygiene hypothesis is not new and is currently used to explain the increasing incidence of allergies and other autoimmune diseases. Because helminths are powerful modulators of the host immune system, it has also been suggested that reduced exposure to helminths due to improved hygiene conditions may favor MS development. In this chapter epidemiological, experimental and clinical data supporting the protective role of helminths in MS are reviewed. Better understanding of host-parasite interactions, as well as identification of specific parasite molecules causing immunomodulatory modulation will help combat allergies and autoimmune diseases without having to pay the price of undesired infectious side-effects.

Keywords: autoimmunity, B cells, environmental factors, Epstein-Barr virus, Experimental Allergic Encephalomyelitis, helminths, hygiene hypothesis, infections, interleukin-10, Multiple Sclerosis, parasites, T cell, Toll-like receptor

Summary

David E. Elliott and Joel V. Weinstock

Inflammatory bowel disease and the hygiene hypothesis: an argument for the role of helminths

Variations in more than 40 genetic loci can alter the risk for developing inflammatory bowel disease (IBD). However, the epidemiology of ulcerative colitis and Crohn's disease suggest that a recent environmental change accounts for most of the disease risk. In this chapter we will introduce IBD and outline its dramatic rise in prevalence over the last 70 years. We will consider the effective eradication of helminths during this time period and the effects of helminths on immunity. We will review the current evidence that helminths induce regulatory immune circuits that suppress aberrant inflammation and may be useful clinically to treat immune-mediated disease.

Summary

Anne Cooke

The Hygiene Hypothesis and Type 1 diabetes

The incidence of some autoimmune diseases is increasing dramatically in the developed world. For example, the incidence of the autoimmune disease, Type 1 diabetes (T1D), is increasing in the UK at a rate of 4% per annum; faster than can be accounted for by genetic change. In the case of T1D, as for many autoimmune diseases, the development of the disease is known to have a genetic component with many genes playing a role in governing the development of disease [1]. However, the development of Type 1 diabetes is not wholly governed by genetics and a role for environmental factors is shown by the 40% concordance rate for development of T1D in identical twins. This lack of 100% concordance in identical twins which is indicative of environmental effects acting on a genetic background is also seen for some other autoimmune diseases such as multiple sclerosis (MS) and systemic lupus erythematosus (SLE). There has been considerable interest in analysing the basis for the dramatic rise in incidence of T1D in the developed world with particular emphasis being placed on the role that infection might play in exacerbating or preventing onset of this autoimmune condition. The evidence that infection may play a role in the prevention of T1D is discussed in this chapter.

Keywords: infection, autoimmunity, type 1 diabetes, Hygiene Hypothesis

Summary

Graham A.W. Rook and Christopher A. Lowry

The hygiene hypothesis and affective and anxiety disorders

Chronic inflammatory disorders are increasing in prevalence in the developed countries. The hygiene hypothesis proposes that our changing microbial environment has resulted in a deficit in immunoregulatory circuits so that there is a failure to terminate inappropriate inflammation. Several stress-related psychiatric disorders, particularly depression and anxiety disorders, are associated with raised levels of proinflammatory cytokines and of other markers of ongoing inflammation, even in the absence of any obvious inflammatory lesion. Moreover proinflammatory cytokines are known to induce depression, which is frequently seen when patients are treated with interleukin-2 (IL-2) or interferon- α (IFN- α). Therefore the occurrence of these psychiatric disorders in developed countries might be partly attributable to a failure of immunoregulation. We review the evidence that inflammation is associated with several patterns of psychiatric disturbance, and that regulatory cytokines such as IL-10 and transforming growth factor- β (TGF- β) can oppose these effects, and that anti-depressants might work in part via effects on inflammation in the periphery.

Keywords: depression, anxiety, inflammation, immunoregulation, regulatory T cells, IL-10, TGF- β , IL-2, IFN- α , gut permeability, tryptophan

Summary

Hafid Ait-Oufella, Alain Tedgui and Ziad Mallat

Immune regulation in atherosclerosis and the hygiene hypothesis

Atherosclerosis is a chronic inflammatory disease of the arterial wall where both innate and adaptive immune responses contribute to disease initiation and progression. The hygiene hypothesis implies that dysregulation of the immune response has led to increased susceptibility to immuno-inflammatory diseases. Recent studies established that subtypes of T cells, regulatory T cells, actively involved in the maintenance of immunological tolerance, inhibit the development and progression of atherosclerosis. Here, we review the immune regulatory pathways of atherosclerosis and discuss the potential implication of pathogens and their associated molecular patterns in the regulation of the immuno-inflammatory response of atherosclerosis.

Keywords: atherosclerosis, immunity, inflammation, lymphocytes, cytokines, infection

Summary

Mel Greaves

The ‘delayed infection’ (aka ‘Hygiene’) hypothesis for childhood leukaemia

The common variant of childhood acute lymphoblastic leukaemia (cALL) is the most frequent paediatric cancer subtype. Its incidence rate appears to have increased substantially in Western societies during the mid-20th Century and continues to increase at ~1%/year. Worldwide cALL appears to track with affluence of societies. The ‘delayed infection’ hypothesis, first formulated in 1988, parallels the hygiene hypothesis and has an evolutionary foundation in the concept of a mismatch between prior genetic selection and programming (of the immune system) and contemporary social circumstances. In essence, the hypothesis predicts that ALL is triggered by an abnormal immune response to one or more common microbial infections and that the abnormality arises for two reasons: (i) infectious exposures being delayed beyond the immunologically anticipated period of infancy; (ii) some degree of inherited genetic susceptibility via, for example, allelic variation in genes involved in the MHC and/or immune response network. The hypothesis also has a framework in the underlying cell and molecular biology of ALL and its natural history. Epidemiological studies of social contacts in infancy (as a proxy for common infections) and risk of ALL provide indirect but strong support for the hypothesis. The idea still requires mechanistic and genetic endorsement and the appropriate studies are in progress.

Keywords: leukaemia, chromosome translocations, polymerase chain reaction, fusion gene, day care, immune network, twins, neonatal blood spots, clusters, evolution, genetics, viruses, transforming growth factor beta, stem cells

Summary

W. Sue T. Griffin, and Robert E. Mrak

Is there room for Darwinian medicine and the hygiene hypothesis in Alzheimer pathogenesis?

Improvements in modern hygiene and public health have resulted in decreased human contact with organisms associated with so-called 'dirtier' environs. These changes, in turn, have led to an appreciation of the potential importance of such 'friendly' organisms toward proper development of the human immune system. Based on this, a novel hypothesis (the hygiene hypothesis) has been formulated. This idea suggests that a paucity of exposure to environmental pathogens retards proper immune system development, and consequently decreases its ability to effectively thwart a variety of effectors with degenerative consequences, such as those associated with chronic inflammatory responses in diseases as seemingly diverse as those of the gut and the brain. In this chapter, we review current information, including the potential contribution of inheritance to development of hypotheses regarding the pathogenesis of chronic neurodegenerative diseases, especially Alzheimer's disease. We further explore ways in which the hygiene hypothesis and ideas in Darwinian medicine may play a role in the neuropathogenesis of these diseases.

Keywords: Alzheimer's disease, Down's syndrome, Parkinson's disease, Creutzfeldt-Jakob disease, Lewy body dementia, cytokines, interleukin-1 (IL-1), tumor necrosis factor (TNF), α -synuclein, amyloid hypothesis, tau hypothesis, cytokine hypothesis

Summary

Margo C. Honeyman and Leonard C. Harrison

Alternative and additional mechanisms to the hygiene hypothesis

The rising incidence of allergic and autoimmune diseases is occurring on a background of genes selected for strong immune responses. Possible mechanisms for selection and changed environmental factors that impact on immune response genes are discussed. Reduced exposure of infants to infections is discussed elsewhere in this volume. Here we consider the role of delayed exposure to infections as well as additional factors that could promote chronic immuno-inflammatory diseases. These include changes in the amount of food consumed, dietary composition, sleep reduction and lower energy expenditure due to reduced exercise and thermoneutrality of the built environment. Any or all of these may result in obesity, which is a proinflammatory state. Increases in air pollution and psychological stress and, finally, insufficiency of vitamin D, are discussed, as these may also shift immune responsiveness towards a proinflammatory state.

Keywords: HLA, Slc11A1, hygiene hypothesis, immunological evolution, environmental factors, diet, obesity, sleep, aryl hydrocarbon receptor, pollution, psychological stress, vitamin D



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