DOHaD 研究（ISSN 2187-2597）
2014 年 第 3 巻 第 1 号 21 頁

【ランチョンセミナーⅠ】
7 月 25 日（共催：JCR ファーマ（株））

Early life environmental determinants of allergic disease: the biodiversity hypothesis and the microbiome

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The global prevalence of allergic diseases is rising to epidemic proportions. While asthma affects 300 million people worldwide, 250,000 people die of asthma every year and 400 million people suffer from allergic rhinitis. More recently atopic eczema and food allergies which affect approximately 200-250 million people worldwide are on the rise (1). In fact, food allergies can result in severe allergic reactions called 'anaphylaxis' that can be fatal. The lack of registries and lack of data on anaphylaxis is of great concern especially as the prevalence of these diseases is increasing in children and adolescents. Furthermore the increasing burden of severe and complex allergies including urticaria, hereditary angioedema, occupational allergies, drug allergies are also of a public health concern.

Asia is the world's most populous continent and the recent International Study of Asthma and Allergies in Childhood (ISAAC III) data shows a rise in the prevalence of allergic diseases in Asia. This trend has resulted in an increase in the disease burden of asthma in developing countries in Asia Pacific. Triggering allergens, climate changes, reduced biodiversity, change in life-styles, dietary habits, hygiene hypothesis are among the various factors contributing to this.
Reduced biodiversity and climate change has been shown to have an adverse impact on human health. However, less attention is given to the effects of reduced biodiversity on the loss on environmental and commensal microbiotas. Commensals are active and essential participants in the development and maintenance of barrier function and immunological tolerance. They are also involved in the programming of many aspects of T cell differentiation in co-operation with the host genome. Studies of healthy individuals and those with disease reveal that reduced biodiversity and changes in the composition of the gut microbiota are associated with a variety of chronic inflammatory diseases like asthma, type I diabetes, inflammatory bowel diseases and obesity. All these inflammatory diseases have shown an increase in prevalence during the past few decades in both developed and developing countries. These alterations in indigenous microbiota and the lack of general microbiota are characteristically associated with the changing life styles towards urbanization. These act as key risk factors for immune dysregulation and impaired tolerance. The risk is further enhanced by lack of exercise and altered dietary habits. Studies

done involving immigrants moving from developing countries to more developed countries have suggested that tolerance mechanisms can rapidly become impaired in microbe-poor environments.

The innate immune system thus provides evidence that physical activity, nutrition, microbiome and various pollutants can influence the development of immune-mediated chronic inflammatory non-communicable diseases (NCDs) like diabetes, obesity, cardiovascular risk, immune diseases, allergies and even mental disorders through Toll-like receptor (TLR) pathways (especially TLR 4). Metagenomic studies demonstrate a significant role for microbiotas in regulating the immune cells that are of relevance to asthma and allergic diseases, such as Th1, Th2, Th17, Treg and dendritic cells as well as TLRs. Common risk factors will provide a platform for potential early intervention across these disease areas and may result in potentially common intervention strategies. With allergic diseases being one of the earliest NCDs to manifest, early intervention for allergic diseases could provide important clues to assess the impact of early interventions and environmental strategies to reduce immune dysregulation and induce tolerance.

While IgE mediated inflammatory mechanisms form the basis of the pathomechanisms allergic diseases, precise mechanisms comprise complex cascade of networks of interactions between immune cells and cytokines as well as epigenetics, there is a crucial need for robust bioinformatic tools for pathway, network and system analyses of epigenetic data and the need to define phenotypes of disease. An integrated and holistic approach for understanding the impact of environment and microbiota on the development and aggravation of allergic disease is crucial and developing modern innovative phenotype-based treatment strategies towards precision medicine is crucial

In the light of this ever increasing burden of allergic diseases and their risk factors, it is important to raise a call to action for global partnerships of multidisciplinary teams involving clinicians, academia, industry, policy makers, patient groups who should work together to raise the awareness and bridge the knowledge gap as well as influence policy decisions that can have a positive impact in addressing this public health issue. The World Allergy Organization's White Book (Update 2013) is targeted towards such a mission

References

1. Pawankar R, Canonica GW, ST Holgate ST et al: *The WAO White Book on Allergy (Update.* 2013)