Parallel Session

Immunology I

THEORETICAL STUDY OF INTERACTION BETWEEN ALLERGY AND INTESTINAL MICROBIOME

Akane Hara

hara.akane32a@gmail.com

Department of Biology, Faculty of Science, Kyushu University, 744 Motooka, Nishi-ku, Fukuoka 819-0395, Japan

Joint work with Yoh Iwasa (Kwansei-Gakuin University)

Keywords: Allergy, Regulatory T cell, Helper T cell, Intestinal microbiome.

Human immune system interacts with intestinal microbiome, the latter forming an ecosystem in the colon. A certain group of intestinal microbiome, for example Clostridium Sp., are known to induce regulatory T cells, abbreviated by Treg, suppressor of exaggerated immune response [1], by producing short chain fatty acid such as butyrate [2]. Hence, the group may be able to suppressor allergy. On the other hand, limited TCR repertoire of Treg cells may cause hypersensitive immune response to commensal intestinal microbiome [3]. A close interaction between immune system and intestinal microbiome suggests us that the distorted composition of intestinal microbiome may lead to the dysregulation of immune system, and that the modification of intestinal microbiome may serve as a treatment of allergy. In this talk, we report our study a simple model for the coupled dynamics of the immune system and intestinal microbe, and we attempt to understand the interaction of the two systems and to find a novel treatment method of allergy by modifying intestinal microbiome condition. We consider the dynamics of regulatory T cells, T helper cells (Th; trigger of allergy), and intestinal microbiome. A portion of the model describes differentiation process of the two types of T cells according to the previous study [4]. The model exhibits three different outcomes: [case 1] a single stable steady state corresponding to healthy state (low level of Th, high level of Treg and high level of microbes); [case 2] a stable steady state for an allergic state (high level of Th, low level of Treg and very low level of microbes); and [case 3] two stable states, each corresponding to healthy state and allergic state, respectively. Considering these three cases, we have two different strategies for suppressing allergy. First, we may eliminate the steady state showing allergy. We derived the condition for [case 1)] where there is no allergy state. Second, we examined the ways to reduce Th level at the allergy state, even if there exists the allergy state. We examined the effectiveness of three microbiome-related parameters (natural growth rate, carrying capacity and Treg induction strength) on suppression of Th and enhancement of Treg. The results showed that Treg induction strength enhancement is the most effective, even if there are few microbes and enhancing carrying capacity of intestinal microbiome allow patients to keep enough microbes to suppress allergy.

Acknowledgements: This work was supported by a Grant-in-Aid for General Scientific Research (B) (No. 15H04423) from the Japan Society for the Promotion of Science to Yoh Iwasa and Leave a Nest Grant Metagen prize to A.H.

References

[1] Sakaguchi, S., Yamaguchi, T., Nomura, T., Ono, M. (2008). *Regulatory T cells and immune tolerance.*, Cell 133, 775-787.

[2] Furusawa, Y., Obata, Y., Fukuda, S., Endo, T. A., Nakato, G., Takahashi, D., Nakanishi, Y., Uetake, C., Kato, K., Kato, T., Takahashi, M., Fukuda, N. N., Murakami, S., Miyauchi, E., Hino, S., Atarashi, K., Onawa, S., Fujimura, Y., Lockett, T., Clarke, J. M., Topping, D. L., Tomita, M., Hori, S., Ohara, O., Morita, T., Koseki, H., Kikuchi, J., Honda, K., Hase, K., Ohno, H. (2013). *Commensal microbe-derived butyrate induces the differentiation of colonic regulatory T cells.*, Nature 504, 446-50.

[3] Nishio, J., Baba, M., Atarashi, K., Tanoue, T., Negishi, H., Yanai, H., Habu, S., Hori, S., Honda, K., Taniguchi, T. (2015). *Requirement of full TCR repertoire for regulatory T cells to maintain intestinal homeostasis.*, Proc Natl Acad Sci U S A 112, 12770-5.

[4] Hara, A., Iwasa, Y. (2017). *When is allergen immunotherapy effective?*, J Theor Biol 425, 23-42.

Parallel Session

Immunology I

BOTH HIGH AND LOW AFFINITY INTERFERONS NECESSARY FOR EFFECTIVE IMMUNE RESPONSE: A MATHEMATICAL MODELLING APPROACH

Arran Hodgkinson

arran.hodgkinson@umontpellier.fr

DIMNP, Université de Montpellier, Campus Triolet, Montpellier, France

Joint work with Ovidiu Radulescu (DIMNP), Gilles Uzé (DIMNP)

Keywords: Mathematical Modelling, Immunology, Structured Models.

Clusters of interferon (IFN) producing cells self-regulate their synthesis of this cytokine through two primary mechanisms: Production of high affinity IFNβ is upregulated by, and low affinity IFNα is dependent upon, the binding of IFNβ to its receptors (IFNAR) 1 and 2 and upregulation of IFN stimulated gene (ISG) expression. Further, the upregulation of ISGs, such as USP18, will initiate a negative feedback loop, downregulating the binding of IFN ligands. The existence and purpose of these high and low affinity IFN proteins, however, remain unresolved in mechanistic biology.

In order to establish the roles that each of these IFN strains play, we produce a novel mathematical PDE model with cells that produce only IFNα, IFNβ, or both proteins. To achieve this, we utilise a previously derived higher dimensional framework [1, 2], representing the spatial distribution of cellular, molecular, and viral populations, through a variable x; the binding of free molecules to a cellular population, through y; and the alteration of the cells internal metabolic dynamics, through α. This allows one to understand not only the overall effect of these interaction but also the underlying dynamics which elucidate the biological significance of each of these disparate proteins.

Results show that cells who could only produce IFNβ were able to sustain their own activity but were unable to communicate this signal to distant clusters. Cells who are incapable of producing IFNβ showed an ability to communicate the IFN signal, under constant stimulating with IFNβ, and potentiate metabolic activity in receiving cells but were incapable of activating these distant clusters. Cells capable of producing both IFNs were able to sustain their own activity and activate distant clusters, more quickly than the advancing virus.

These results suggest that both high and low affinity IFN play essential roles in activating and propagating the immune response in advance of a proliferating virus, conferring an evolutionary advantage to the host of a dual-IFN system. The use of higher-dimensional systems of PDEs allows us to reveal that the potentiation of underlying pathways, involved in the transcription of ISGs, in peripheral cells, allows for the efficient initiation of the anti-viral response in these cells and the local immune system.

References

[1] Domschke P, Trucu D, Gerisch A, Chaplain M A J. (2017) *Structured Models of Cell Migration Incorporating Molecular Binding Processes.* Journal of Mathematical Biology **75**(6-7):1517-1561

[2] Hodgkinson A, Uzé G, Radulescu O, Trucu D. (2017) *Signal propagation in sensing and reciprocating cellular systems with spatial and structural heterogeneity.* Manuscript submitted for publication

Parallel Session

Immunology I

KINETICS OF INNATE IMMUNITY WITHIN THE CELL: MATHEMATICAL PARALLELS WITH PRIONS

Sophie Ip

si279@cam.ac.uk

Department of Applied Mathematics and Theoretical Physics, University of Cambridge, Cambridge CB3 0WA, UK

Joint work with Julia R. Gog (Department of Applied Mathematics and Theoretical Physics, University of Cambridge), Clare E. Bryant (Department of Veterinary Medicine, University of Cambridge) and Lee J. Hopkins (Department of Veterinary Medicine, University of Cambridge).

Keywords: Innate immunity, Prions, Ordinary differential equations.

The inflammasome is a large protein complex that plays a vital role in innate immune signalling. Despite its importance, the mechanisms of inflammasome formation remain controversial on the basis of experimental observation, and there are very few existing mathematical models of this process. However, the protein constituents of the inflammasome have often been compared to prions, which are the subject of an extensive modelling literature. In particular, a 'nucleated polymerisation' mechanism has emerged as the favoured conceptual model of prion propagation, through mathematical modelling consolidating experimental work.

Here I will present collaborative work with immunologists in which we explore inflammasome formation through a similar process of iterative modelling and experimental work. In particular, we have adapted prion nucleated polymerisation ODE kinetic models to create a suite of models describing hypotheses for inflammasome formation mechanisms. By comparing these models to experimental results, and conducting novel laboratory experiments in tandem, we have a powerful approach to gain new insights into how innate immunity works.

Parallel Session

Immunology I

CHARACTERIZATION OF CTLA4 TRAFFICKING: A COMBINED *IN SILICO* AND *IN VITRO* APPROACH

Sahamoddin Khailaie

khailaie@theoretical-biology.de

Department of Systems Immunology and Braunschweig Integrated Centre of Systems Biology, Helmholtz Centre for Infection Research, Rebenring 56, D-38106 Braunschweig, Germany.

Joint work with Behzad Rowshanravan (Institute of Immunity and Transplantation, University College London Medical School, London, UK), Philippe A. Robert (Department of Systems Immunology and Braunschweig Integrated Centre of Systems Biology, Helmholtz Centre for Infection Research, 38124 Braunschweig, Germany), Lucy S. K. Walker (Institute of Immunity and Transplantation, University College London Medical School, London, UK), David M. Sansom (Institute of Immunity and Transplantation, University College London Medical School, London, UK) and Michael Meyer-Hermann (Department of Systems Immunology and Braunschweig Integrated Centre of Systems Biology, Helmholtz Centre for Infection Research, 38124 Braunschweig, Germany and Institute for Biochemistry, Biotechnology and Bioinformatics, Technische Universität Braunschweig, Braunschweig, Germany).

Keywords: CTLA4 trafficking, Transendocytosis, Co-stimulation, Regulatory T cells.

Costimulatory ligands (CD80 and CD86) expressed by antigen presenting cells (APC) are essential for T cell activation. Cytotoxic T-lymphocyte-associated protein 4 (CTLA4) is an essential regulator whose biology is key to the function of regulatory T cells and immune tolerance. CTLA4 molecules, mainly expressed by regulatory T cells, control the stimulatory capacity of APCs by a process of transendocytosis whereby CTLA4 physically removes its ligands, CD80 and CD86, from APCs and degrades them in lysosomes. Transendocytosis, therefore, allows CTLA4-expressing T cells to quantitatively control the expression level of CD80/CD86 and thereby limit T cell activation. The capacity of CTLA4-expressing T cells to limit immune responses depends on a complex series of parameters including CTLA4 expression levels, trafficking between cytosol, plasma membrane, and lysosomes. By combining *in vitro* experiments and mathematical models, we characterized CTLA4 trafficking and its link to the efficiency of ligand uptake. Surprisingly, extremely stable CTLA4:ligand binding does not guarantee efficient ligand uptake; instead we identify an optimal range of off-rates for this process. Our model predicts the importance of an intracellular pool of CTLA4 for rapid functional activity and the dominance of CD80-CTLA4 interactions. Knowledge of the trafficking parameters of CTLA4 is key to scheduling therapies targeting the co-stimulation machinery of T cells. Further, the developed mathematical model provides a framework which may be used to understand and predict the impact of CTLA4 mutations that alter its affinity or pathway mutations impacting its trafficking behavior.

The presented combined *in vitro* and *in silico* strategy of extracting essential trafficking parameters of transmembrane molecules, which are not easily accessible to experiment, may be applicable to other molecules.