Satellite Meeting on Theoretical Immunology

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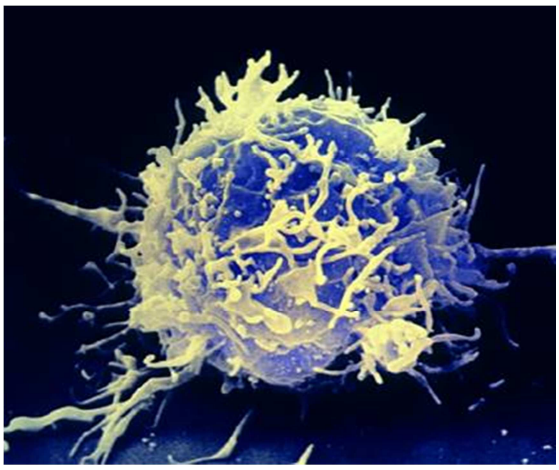
Modelling the Complexity of the Immune System



Book of abstracts

Carmen Molina-Parìs, University of Leeds

Stochastic modelling in immunology at the molecular, cellular and population levels

T-cells sense their environment by means of T-cell receptors (TCRs) on their surface. A T-cell expresses about 30,000 copies of a unique (clonotypic) TCR, whose ligands are complexes composed of a peptide bound to an MHC molecule (pMHC). In vivo, TCR ligands are expressed on the surface of antigen-presenting cells (APCs). In the thymus a variety of professional APCs will subject immature T-cells (or thymocytes) to a "double test" by displaying a wide range of pMHC complexes, with peptides derived from household proteins (self-peptides). The stochastic nature of gene rearrangements implies that some TCRs will not be able to recognise a self-pMHC ligand (TCRs that are not functional) and that others will recognise it far too well, and thus would give rise to mature T-cells with the potential to generate autoimmune responses. Thus, the need for a double test that will check the functionality of a thymocyte (positive selection) and its state of tolerance, so that it does not recognise self-pMHC complexes with high affinities (negative selection). This thymic selection process only allows 2-5% of thymocytes to become mature T-cells. We have made use of mathematical modelling to address the following questions: (1) at the receptor level, what are the time scales for T-cell responses, (2) at the cellular level, what is the threshold number of APCs in a given lymph node needed to initiate an immune response, and (3) at the population level, how is T-cell clonotype size and diversity homeostatically regulated.

Ulrich Behn, University of Leipzig

Evolution towards a complex architecture and self-tolerance in a minimal model of the idiotypic network

In our minimal model of the idiotypic network a node represents a clone of B-lymphocytes of identical idiotype which is encoded by a bitstring. Nodes of complementary idiotype, allowing a few mismatches, are linked. The model includes the influx of new, randomly generated idiotypes and a negative selection of not sufficiently or over-stimulated clones. The network evolves towards highly organized modular architectures, where the nodes can be classified into groups according to their statistical properties. The building principles of these architectures can be analytically described. The most interesting architecture comprises a densely linked core, a weakly connected periphery, groups of unoccupied nodes, and singletons. In the presence of permanently occupied nodes, playing the role of self, the architecture evolves in such a way that the expansion of autoreactive clones is controlled by the network, thus providing self tolerance. A modular mean field theory describes the statistical properties in good agreement with simulations. The results are discussed in the immunological context.

Rossana Scrivo, Sapienza University of Rome

Autoimmune phenomena of biological treatments

Cytokines mediate many aspects of immune function; they are produced by activated immune cells, and either enhance or inhibit the immune response. Their multiple activities are regulated mainly at the level of their secretion by expression of their receptors, by the concomitant action of several cytokines, and by the occurrence of inhibitory proteins and specific carrier molecules. In the last two decades, manipulation of the cytokine milieu by administering targeted therapy has become the cornerstone of biological therapies, which have proven to be an effective treatment modality in most patients with inflammatory rheumatic diseases resistant to conventional drugs. Later, novel biologic treatments recognizing other molecular or even cellular targets have been introduced into the clinical practice. Curiously, all of them may be associated with autoimmune phenomena, including the development of autoantibodies and of autoimmune clinical manifestations. The talk will cover the spectrum of autoimmune phenomena associated with biological therapies.

Pietro Liò, University of Cambridge

Assessing comorbidities risk during an infection: SARS and HIV case studies

Comorbidity is a research area of great cross-disciplinary interest, but it is defined mainly in the medical/clinical setting. However, the role of comorbidity is relatively unexplored in comparison to that of individual diseases. Moni's research presents an approach of quantitative framework to compare and explore the comorbidities arising from an infection. This approach estimate the prevalence, association and risk scores of the disease multimorbidity based on the available gene expression, gene diseases association, protein-protein interaction (PPI), signaling pathways and phenotypic disease correlation data. Two case studies SARS and HIV-1 infections are presented to investigate the comorbidities association with other human diseases.

Elena Agliari, University of Parma

Anergy and parallel processing in spin glass models of immune networks

We present some recent investigations on systemic features of the immune system, *based on a statistical mechanics approach. After a streamlined introduction on the (adaptive response of the) immune system, we introduce a spin-glass model for the interaction between T lymphocytes and B lymphocytes; such a model is able to mimic, as emerging properties, several collective phenomena shown by real systems (e.g. the self/non-self distrimination, the breakdown of immunosurveillance by lymphocyte unbalance, the capability of fighting several pathogens simultaneously). We also show that this system can be mapped into a (multitasking) associative network, where T cells directly interact with each other and are able to orchestrate an immune response retrieving (several)"strategies" previously learnt. Lastly, we aim to show that anergy (experienced by self-directed B-cells escaped from clonal deletion at ontogenesis) shown via the idiotypic network à la Varela is in agreement -and not conflicting- with the more recent two-signal model perspective.*

Susan Holechek Arizona State University

Dengue as a complex epidemiological and immunological system

Dengue is one of the most severe and under-diagnosed vector-borne diseases in the world threatening two-fifths of the world population. Fifty to one hundred million infections are reported every year including approximately 500,000 severe cases due to dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS), and 22,000 deaths, involving mostly children. The increase in the number of DHF and DSS cases during the last decade calls for interdisciplinary efforts between experimentalists, epidemiologists and modelers in order to fight dengue at different scale levels. We propose an epidemiological model that captures disease progression and a within-host model that captures the viral dynamics upon a secondary infection with a heterologous dengue virus serotype with the aim of understanding the antibody-dependent enhancement mechanism of virus replication, considered the lead cause of the more severe dengue disease forms DHF and DSS. Our parameters are based on immunological and epidemiological data from dengue outbreaks in which the population was susceptible to the invasive dengue-2 Asian genotype, which has been found to have replaced dengue-2 American in several countries and has been associated with DHF cases. Our models are built on the observation that following infection with dengue-1, individuals generate antibodies that will protect them against secondary infection with dengue-2 American but not dengue-2 Asian suggesting that the affinity of neutralizing antibodies plays a crucial role in the development of DHF. The understanding of the complexity of dengue at both the epidemiological and immunological scale will allow us to create a nested model that links the within- and between-host dynamics of the disease providing a better insight into the onset of dengue outbreaks.

Anna Alemany, Universitat de Barcelona

Bond elasticity controls molecular recognition specificity in antibody-antigen binding

Force-spectroscopy experiments make it possible to mechanically characterize immuno-chemical reactions at the level of single ligand-receptor pairs. Here we describe a methodology to measure the correlation between bond strength and flexibility in systems of polyclonal and monoclonal antibodies using optical tweezers. We observe that polyclonal antibodies obtained after immunization with methyl-boldenone establish more rigid interactions than the ones obtained before immunization. We also test the ability of a monoclonal antibody, designed to specifically recognize boldenone, to cross-react with testosterone. We find that monoclonal antibodies still recognize testosterone but with lower affinity as revealed by the spectrum of bond rigidities and strengths, which suggests that antibodies explore different conformations to improve molecular recognition. Our approach suggests that bond flexibilty plays a major role in remodeling antibody-antigen bonds in order to improve recognition during the maturation of the humoral immune system.

Marcello Delitala, Politecnico di Torino

A mathematical model of competition between cancer cells and T-cells under immunotherapy

How does immunotherapy affect the evolutionary dynamics of cancer cells? Can we slow down cancer evolution by using immune boosters? Bearing these questions in mind, we present a mathematical model of cancer-immune competition under immunotherapy. The model consists of a system of structured equations for the dynamics of cancer cells and activated T-cells. Numerical results suggest that the selection of proper infusion schedules may play a key role in the success of anti-cancer therapies.
In particular, we highlight how cancer evolution can be effectively slowed down by immunotherapeutic protocols relying on successive infusions of agents that boost the proliferation of activated T-cells and agents that enhance immune memory.

Deborah Dunn-Walters, King's College London

Challenges of age in immune system

A healthy immune system is essential for healthy ageing. In addition to protection from external pathogens, the immune system needs to maintain tolerance towards self antigens and protection against tumours. Thus it is a complex and balanced system, with strong homeostatic control. Unfortunately the balance is lost with age.
Not only are older people more prone to infection and cancer, but they have increased levels of autoantibodies and circulating inflammatory mediators. Many elements of the system have been investigated and found to be impaired with age. In our studies of B cells we have found that the repertoire of B cells is perturbed with age, osing the diversity that is such an essential feature of the adaptive immune system. Our studies on repertoire have been carried out using B cell spectratyping and, more recently, high throughput sequencing. Following the immune response after challenge with commonly administered vaccines we find significant age-related changes in IgA and IgM antibodies, indicating that vaccine design for older people needs to address production of antibodies other than IgG. Looking at antibody repertoire in sorted populations of B cells we see that age-related differences are subclass-specific. Our data appear to suggest that age-related differences differ between types of B cell. Better standards for defining functional B cell populations will be required in order to fully understand the changes observed.

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