seems to fulfil the unmet need that this area of infectious diseases has felt for sometime now, especially with the emergence of HTS technology. The authors give a detailed account of what is expected when an emerging pathogen is suspected, beginning with appropriate sample collection/preparation and suitable molecular methods for their detection. Chapter 14 on genomics of major histocompatibility complex (MHC) and human disease, offers the reader a comprehensive view on MHC and its association with human diseases. The concept of linkage disequilibrium (LD) is well narrated since it is important in association studies as MHC is known to have strong LD blocks and as pointed out, the MHC region has more association with human disease than any other region of the genome. Chapter 15 enlightens the readers on 12 immune-related disorders, which have been subject to GWAS and/or are part of the Immunochip consortium studies. Further, data is used from these studies to analyse functional significance of GWAS hits and perform pathway analysis. Moreover, the chapter gives a good background on genetic studies in immune-mediated disorders beginning with candidate gene studies, linkage studies; it extensively discusses GWAS, interpretation of GWAS hits, functional variant discovery and pathway analysis to understand disease biology.

Activating somatic mutations in the RAS gene family are oncogenic drivers in cancer. Chapter 16 deals with rasopathies, which are a defined group of medical genetic syndromes arising due to germline as opposed to somatic mutations in RAS genes and their pathways. Rasopathies are the largest known group of malformation syndromes affecting 1 in 1000 individuals. Some, but not all individuals, have an increased risk of cancer in various organs. Despite advent of genomic technologies and several drug trials, not all mutations leading to rasopathies have been identified, nor have all potential drugs been evaluated in clinical trials. Clearly, it is important to study these syndromes in greater detail to help define the best medical practices for each Rasopathy.

Genomic dissection of complex traits and associated diseases are well articulated in several chapters of this book. Complex diseases such as autism spectrum disorders, degenerative disc disease and osteoarthritis and melanoma have been discussed in chapters 9, 11 and 12 respectively. In connection with this, chapters 19 and 20 deal with two timely topics of quantitative traits dissection in mice and power of meta-analysis in GWAS. Both these chapters essentially discuss the advancement of statistical methodology to deal with high-resolution mapping in association studies. The take-home messages like 'statistical methods that combine haplotype mapping with near-complete catalogs of sequence variants segregating among inbred mouse strains, make it possible to test whether individual variants are functional' or 'larger GWA meta-analyses, could increase our knowledge by identifying new loci, thus increasing the proportion of variance explained and potentially also providing new insights into the biology of human disease' point towards a routine practice of these statistical methods as independent genomic research groups will publicly share data to form worldwide consortia.

A number of ethical issues are also included in this volume. In chapter 24, the authors discuss the trend of using pediatric-whole genome sequencing (P-WGS) and pediatric-whole exome sequencing (P-WES) for testing in children. Though genetic testing in children for some conditions is common, due to a huge drop in cost and time taken for WGS/WES, it is fast becoming an affordable and routine clinical option. Currently, WGS/WES is done as a part of research studies in childhood health conditions, or in children with serious undiagnosed health conditions to understand disease causation. Parents now express interest in obtaining genetic health information of their children and ask for provisions in pediatric care. However, the impact of knowing test results on children and their families, the mode of communication of such results by health professionals, clinical care decisions and reporting incidental findings that the children were not tested for which are revealed due to the genome-wide nature of sequencing, remain under studied. These are therefore major challenges which need to be overcome at the policy level, before routine adoption of such testing in pediatric care. It is evident that before implementation, P-WGS and P-WES must be proven to be more advantageous over existing tests in terms of accuracy and efficiency; it must contain actionable information that can ultimately improve overall health outcomes in children. More research needs to be focused on parental choice, return of test results, impact on children and families, supporting research at the infrastructural level, clinical training and policy making in order to adopt P-WGS/P-WES in pediatric healthcare practice.

Finally, this volume is a perfect and timely compilation review articles pertinent to human genetics and genomics. Investigators in the respective fields would definitely find this as a useful reference.

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Annual Review of Immunology, 2012. William E. Paul, Don R. Littman and Wayne M. Yokayama (eds). Annual Reviews, 4139 El Camino Way, P.O. Box 10139, Palo Alto, CA 94303-0139, USA. vol. 30. xi + 822 pp. Price: US$ 94.

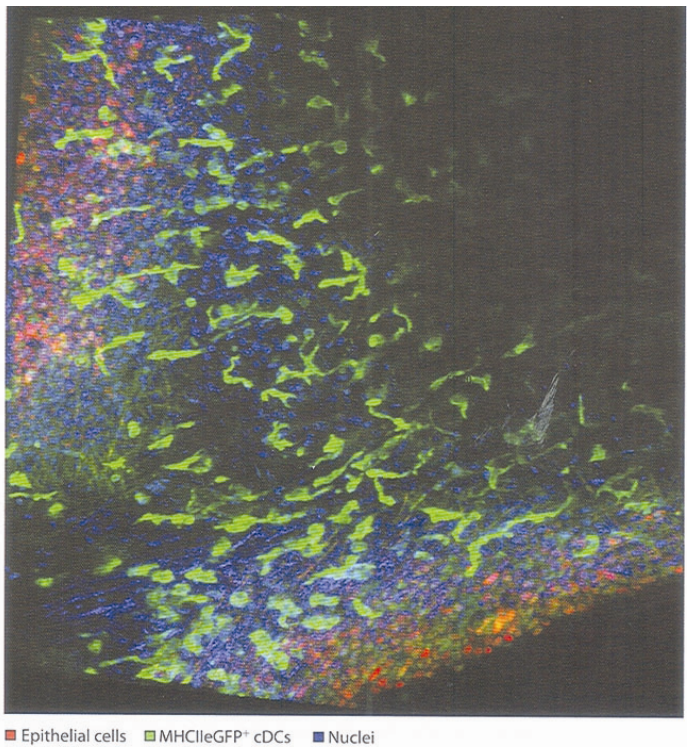
Each year the *Annual Review of Immunology* (*ARI*) puts together a series of excellent reviews by leaders in the field in different areas of immunology. This volume is no different and areas covered can be broadly classified under distinct topics: immune cells and their biology, regulation of immune responses, etc.

The arsenals used by the adaptive immune responses in vertebrates are diverse. Jawed vertebrates utilize the B-cell receptor, T-cell receptor and major histocompatibility complex encoded molecules, whereas variable lymphocyte receptors (VLRs) play an important role in jawless vertebrates, e.g. lampreys and hagfish. VLRs consist of an array of leucine-rich repeats (LRRs) and consist of two broad types. The number of LRRs is variable with the sequences being highly divergent. VLRA is expressed on T cells, whereas VLRB is expressed on B cells and secreted as a multivalent protein. Interestingly, VLRA is expressed on thymus-like tissue present at the tip of gill

filaments, whereas VLB is expressed in hematopoietic tissues. It is considered that the assembly of VLRs is by a gene conversion process, involving activation-induced cytosine deaminase.

Neutrophils are the most abundant white blood cells in circulation and different aspects of neutrophil biology have been discussed in detail. Recent studies have shown that neutrophil extracellular traps, which are antimicrobial extracellular chromatin structures produced during cell death, are associated with autoimmunity, e.g. systemic lupus erythromatosis. The thymus is important for the generation of $CD4^+$ and $CD8^+$ T cells, which are critical for the cellular immune response. There is a detailed review summarizing the roles of the thymus in generating other types of T cell subsets, e.g. invariant natural T cells, natural regulatory T cells, natural T cells expressing IL17 and $CD8^+$ alpha expressing intraepithelial lymphocytes. Regulatory T cells are important in the modulation of cellular responses. These cells were identified around 1995 and shown to be important in reducing autoimmunity. Broadly, there are two types of regulatory T cells: natural, i.e. generated in the thymus and induced, i.e. generated during an immune response as part of the regulatory processes. Much has been learnt about their generation and the factors regulating them in the thymus and periphery. Interestingly, microarray analysis has revealed complexity in the patterns present in regulatory T cells present in different organs.

The discovery of gut organisms regulating the number of regulatory cells and lowering inflammatory responses to ensure their co-livelihood with the host, makes for interesting reading on symbiosis. The inhibition of the mammalian target of rapamycin (mTOR), an evolutionary conserved serine–threonine kinase, increases the number of regulatory T cells, and this approach together with other strategies may lead to long-term tolerance to transplants. In fact, clinical trials are in progress to evaluate the roles of regulatory T cells in the suppression of immune responses, e.g. during graft versus host disease. However, several issues need to be taken into account, e.g. the consistency of these cells as regulatory T cells, altered differentiation into effector cells that may be pathogenic, etc.



A highly developed network of $MHCIIeGFP^+$ conventional dendritic cells (cDCs) is found in the epithelial layer (red) of the trachea. These DCs form long cellular extensions that run in between the basolateral space made up of basal epithelial cells. Nuclei were counterstained with DAPI (blue).

Autophagy is a response by cells to nutrient deprivation. Recent studies have shown that oxidative stress, immune cell activation, etc. also stimulate autophagy. In fact, genes involved in autophagy are linked to inflammatory diseases, e.g. Crohn's disease. The role of mTOR in integrating environmental cues with cellular functions has been reviewed. In activated T cells, mTOR plays an important role in anabolic processes by enhancing glycolysis, glucose uptake, the pentose phosphate pathway, fatty acid and sterol synthesis. The importance of micro-RNA in the expression of important genes involved in the immune response has been reviewed, e.g. mir-155 regulates the expression of important transcription factors like PU.1 and SOCS-1. The link between inflammatory responses and cancer has been discussed in great detail. Changes in modern life and diet, have led to increase in body mass and excess weight is associated with increased severity to various diseases, including diabetes and cancer. The molecular mechanisms include the enhanced production of inflammatory cytokines with increase in mitochondrial ROS by adipose tissues. A study has shown that in patients taking aspirin, a non-steroidal anti-inflammatory drug, which inhibits the production of prostaglandins, it also lowers the incidence of cancer. The author suggests that inflammation should be added as the seventh hallmark in addition to the previous six markers of cancer identified by Hanahan and Weinberg in 2011.

There are two ways by which the immune system attempts to deal with microbes: removal, i.e. their elimination and tolerance, i.e. learning to live with these bugs. Most studies have focused on the arsenals that are required for the first part. An excellent article by Ayers and Schneider recounts examples on how these mechanisms exist in different organisms. For example, the pea aphid lacks some genes involved in the sensing of peptidoglycan. Consequently, it is oblivious to the existence of a symbiotic bacterium, *Buchera aphidocola*. Also, it is well known that the gut flora boosts the mucosal immune system. In fact, two reviews have discussed the role of the host response to gut microflora. This aspect is of importance as there are approximately 10^{14} microorganisms present in the gut of each human being. Consequently, the microbes present in the gut

environment influence host responses; for example, changes in the gut microflora are associated with inflammatory bowel disease.

There are two personal articles that may be useful to readers interested in the history of immunology. The first one is by Fritz Melchers on the Basel Institute of Immunology (BII), Switzerland, which was a cradle for creative research in immunology from 1971 to 2000. Of note, Susumu Tonegawa (Nobel laureate in 1987) demonstrated the rearrangement of immunoglobulin genes while working in BII. What are some of the reasons responsible for the amazing success of BII? First, scientists were free to work on areas of their choice for four years before taking up more permanent positions in other institutes. Scientists were fully independent with their own budget, laboratory space and access to central facilities. The high turnover ensured constant influx of new ideas in a fast-moving field. Incidentally, BII followed a 'zero growth' policy with respect to personnel and the total number of staff hovered around 215, including 65 scientists, per year. Second, there was a lack of hierarchy and the title of all scientists was 'Scientific members'. Third, scientists were encouraged to dwell on the concepts and theories in immunology. Before a manuscript was to be submitted, the work was presented as a seminar and two members from within BII reviewed the same. Fourth, well-trained technicians manned the central facilities. Finally, the cafeteria was open all day, which was a prime site for informal discussion on science and life. This institute was fully funded by Roche; however, following the elucidation of the human genome, the company decided to close down BII in 2000 and reappropriate funds into medically applied genome research. The article is insightful on the traits that are required to build and sustain an institute devoted to excellence in immunological research.

The prefatory article is by Ralph Steinman, the 2012 Nobel laureate, who passed away days before the announcement of the award. His reading of M. Burnet's *Clonal Selection Theory*, which was published in 1959, led him to ask the key question: how are immune responses initiated? Steinman has discussed his journey on the identification and possible translation outcomes of dendritic cells (DCs), the key initiators of the cellular immune response. Three choices appear to have tilted the balance in his favour: First, the close support that he received from his mentor, Zanvil Cohn. Second, the ability to work in Rockefeller University, USA, which is well known for research related to cell biology. Third, working with spleen cell suspensions compared to peritoneal cells which were used by other members of the Cohn laboratory – perhaps, it pays not to follow the herd! Intriguingly, Steinman started his research with a commitment to try and decipher as to how the T cell response was initiated. At that time, he did not have a hypothesis and wondered as to how his grant AI13013 was initially funded as there was no way to realize that DCs would be key antigen presenting cells. Interesting, this grant has been continuously funded for 36 years. He observes: 'funding should be determined by what the investigator brings to the table from his or her past work and the importance of the problem he or she chooses to study. It is simply illogical to award funds for a feasible and detailed future approach in which case the biological unknown is likely doomed to be incremental'. In addition, Steinman expressed the view that he dislikes the distinction between basic and clinical immunology. 'Research on disease and in patients are both basic… research attempts to uncover the unknown whether it is clinical, cellular or molecular'. Readers are encouraged to read this volume for more such gems and information on the facets on the immune system.

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