Moraceae) and *Nageia wallichiana* (C. Persl) Kuntze (a Gymnosperm, the only wild conifer of South India with male cones in pedunculate clusters and solitary female cone, Podocarpaceae) are included. Under hitchhikers (adopted for dispersal of fruits by a variety of animals), *Bhesa indica* (Bedd.) Ding Hou (evergreen tree with white flowers and prominently 2-lobed capsules, Centroplacaceae), *Semecarpus travancorica* Bedd. (endemic to the southern Western Ghats, Anacardiaceae), *Dimocarpus longan* Lour. (a tree species that produces edible fruits, Sapindaceae), *Trichilia connaroides* (Wight & Arn.) Bentv. (tree with compound leaves, bisexual flowers and a globose, bright red, capsule with an arillate seed, Meliaceae), *Actinodaphnae malabarica* N. P. Balakr. (smaller tree, branchlets rusty with simple, subverticillate leaves, flowers in fascicles and fruit black, 1-seeded, Lauraceae), *Cinnamomum malabatrum* (Burm. f.) J. Persl (tree, tri-nerved leaves young bright pinkish tinged with yellowish-green, and mature ones dark green, distinct thalamus-based fruits green, purple when ripe), *Litsea oleoides* (Meisner) Hook.f. (tree, leaves simple, flowers in racemes, fruit depressed globose, 1-seeded, Lauraceae), *Persea macrantha* (Nees) Kosterm. (known to be medicinal, commercially important tree for its bark, native to Western Ghats and Sri Lanka, Lauraceae) and *Ormosia travancorica* Bedd. (an endemic tree with distinct scarlet seeds, Leguminosae) are included. Under wild Rudraksha (treated separately for having religious significance), three species namely *Elaeocarpus munroii* Mast., *E. serratus* L. and *E. tuberculatus* Roxb. are included. Under stranglers included are *Ficus macrocarpa* L.f. and *F. tsjahela* Burm.f. (inappropriately, the keystone species had gone into stranglers group!). The species namely, *Bombax insignae* Wall., *B. ceiba* L., *Vernonia arborea* Buch.-Ham., *Toona ciliata* M. Roem. and *Heritiera papilio* Bedd., with majority of them having samaroid fruits, have been placed under 'blown in the wind group' (wind as medium of dispersal). The group representing sun trees (plants that appear as pioneers in sun-lit gaps of rain forests) are *Mallotus tetracoccus* (Roxb.) Kurz and *Sterculia guttata* Roxb.

Sartaj Ghuman has drawn five beautiful pen sketches of Anamalai landscapes with buildings and trees of *Ficus*, Mango, *Erythrina*, probably *Eucalyptus*? and *Prunus ceylanica* in the book. The front and back covers of the book are decorated by *Canarium strictum* and *Elaeocarpus munroii* respectively. The book is dedicated to the 'Trees – the original landscape historians' and true to the caption, trees are real mute witnesses to all events that happen in their surroundings. The book was published by Trail Blazer India Private Limited, Bangalore, on recycled chlorine free paper. It is a welcome gesture of Nature Conservation Foundation that they intend to distribute this book *free* to schools and colleges, plantation managers, and forest officers/staff for the cause of awareness and conservation of these prominent trees of Western Ghats. The excellent production standards further add to its merit to be on the reference shelves of every serious botanical artist and artists with experience and skill in drawing and painting of plant habit sketches, flowers and fruits.

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As every year, this authoritative collection covers recent advances in immunological science. Increasingly, fresh insights into hitherto undiscovered immunological processes are powered by the emergence of new technologies and approaches. This is an exciting time: The interval between an advance in the basic understanding of immune dysfunction and the emergence of potential therapeutics is shrinking, which augurs well for interventions aimed at bettering the human condition. Apologies are due to authors whose excellent work we could not review due to space constraints.

As Boehm *et al.* (pp. 19–42) discuss, the study of the nature of immune defence in jawless fish (lampreys and hagfish) is instructive from an evolutionary standpoint, because these organisms are considered representative of early vertebrates. After early experiments demonstrating the generation of immunological responses (in the form of ≅ 300 kDa antibody-like 'agglutinins') subsequent to immunization with foreign moieties, injecting lampreys with plant mitogens and antigens has helped enumerate the presence of membrane-bound variable lymphocyte receptors (VLRs). The highly diverse sequences that characterize such VLRs comprise invariant N- and C-terminal regions flanking intervening regions of variability. Three VLR isotypes have been characterized (VLRA, VLRB and VLRC), with each lymphocyte expressing one *VLR* gene on account of allelic exclusion, indicating a pattern of clonal antigen receptor expression akin to that seen in jawed vertebrates. While VLRBs are secreted from cells after antigen stimulation (as antibodies are from B cells in jawed vertebrates), VLRAs and VLRCs remain cell-bound (as do TCRs in jawed vertebrates).Precise mechanisms of negative selection that enable tolerance to self-grafts remain unknown. While two genes (*CDA1* and *CDA2*), putatively encoding activation-induced deaminases, have been described in lamprey, formal proof of their involvement in gene conversion-like events is awaited. The antibody-like agglutinins that are generated upon immunization can fix complement to lyse target cells. Several cytokine and their receptors have been discovered, and downstream effects are being discerned. Parallels between components of adaptive immunity between jawed and jawless vertebrates are suggestive of the existence of a common vertebrate ancestor.

Bangam (pp. 43–71) discusses current knowledge on the biology of human T cell leukemia virus Type 1 (HTLV-1). Interestingly, disease manifests in only an estimated 5–10% of people who are infected. Viral transmission occurs via sexual intercourse, or upon transfusion with infected blood products; vertical transmission through breast milk is also considered a significant mechanism of

transmission. Adult T cell leukemia/lymphoma (ATL) and HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM) are two diseases most commonly associated with HTLV-1 infection, as are uveitis and polymyositis. Prognosis in patients is poor; while AZT and IFN-α are often employed as therapy, some success has been achieved with stem cell transplants. The onset of HAM can be insidious, with symptoms including back pain, incontinence and erectile dysfunction. Infection can also increase predisposition to infection with other organisms like *Mycobacterium tuberculosis* and *Staphylococcus aureus*. Interestingly, different pathological outcomes of infection are not associated with specific HTLV-1 genotypes. It appears that propagation of the virus *in vivo* occurs via cell-to-cell contact, mediated upon formation of a virological synapse. Integration in chromosomes 13, 14, 15, 21 and 22 appears to carry a significant survival advantage, the reasons for which remain unclear. Virally induced proliferation of infected cells, rather than *de novo* infection, appears to be primarily responsible for persistence. Curiously, infected cells carry an abundance of phenotypic markers (including FoxP3) that are characteristic of T reg cells, the relevance of which is currently unclear.

The process of transport of cytoplasmic components to the lysosomes via double-membrane bound vesicles (the autophagosomes) is referred to as autophagy. Matsuzawa-Ishimoto *et al.* (pp. 73–101) outline advances in the understanding of this critical process. Autophagy (and autophagy-related events) is implicated in an increasing number of immunological processes, including lymphocyte signalling and antigen presentation. Autophagy is involved in monocyte-to-macrophage differentiation, and dendritic cells employ proteins of the autophagic pathway during antigen presentation. Though autophagic processes are involved in the delivery of viral RNA to the endosomes for the production of interferon, prominent roles for autophagy in the suppression of the secretion of pro-inflammatory cytokines have also been described. ATG16L1 is believed to contribute to intestinal homeostasis, since reduced expression results in intestinal injury upon infection with a commensal virus that is otherwise well-tolerated. A mutant of this protein (which makes it susceptible to caspase-3 cleavage) is associated with an increased risk of Crohn's disease, as well as with higher instances of graft versus host disease after stem cell transplantation. In contrast to its protective effects in inflammatory bowel disease, autophagy is believed to contribute to pathological outcomes in patients of rheumatoid arthritis, possibly linked with its mediation of resistance to apoptosis in CD4 T cells. Survival of antibody-secreting plasma cells appears to be autophagy-dependent, a finding in consonance with higher levels of autophagic proteins in B cell plasma blasts derived from SLE patients and lupus-prone mice. Autophagy protects cells which are stressed. Contrarily, autophagic proteins have also been shown to facilitate death; factors that promote cell survival versus death outcomes are under study. Upon damage to pathogen-containing vacuoles, intracellular pathogens (including both viruses and bacteria) which gain access to the cytoplasm can be sequestered by an autophagy-related mechanism (referred to as xenophagy), an event that aids in immunity. Bacteria appear to have evolved strategies to escape such a fate. Greater understanding of the influences that mediate seemingly contradictory outcomes that the autophagic pathways mediate will drive further advances in the area.

Activation of the adaptive immune system, for the most part, is critically dependent on T cell activation. It is therefore not surprising that a great deal of effort goes into understanding the processes that trigger and mediate this event. Alcover *et al.* (pp. 103–125) provide a historical perspective, while also reviewing recent advances. Though TCR $\alpha\beta$ and TCR $\gamma\delta$ receptor diversity is generated as a consequence of somatic recombination events, these receptors do not experience somatic mutations during an on-going immune response, as do immunoglobulins. Individual TCR-MHC + peptide affinities can be quite low (0.5 μM to 100 μM); other interactions, as well as co-receptor (CD4 and CD8) interaction with the MHC, work to increase overall avidity and stabilize antigen presenting cell–T cell association. TCRs exist on the cell membrane in association with four non-variant chains (γ, δ, ε and ζ), collectively referred to as the CD3 complex. Continuous recycling of the TCR–CD3 complex occurs between the plasma membrane and the endosomal compartment. Incomplete TCR complexes are eliminated, and steady-state levels of active TCR complexes are maintained on resting cells. Upon antigen recognition, TCR–CD3 complex clustering occurs, aided by the fact that TCR-CD3 complexes are redirected to sites of TCR engagement. Conformational and/or mechanical changes upon TCR triggering are 'conveyed' to the CD3 proteins, making the ITAM motifs in CD3ζ and CD3ε chains amenable to phosphorylation via CD4- or CD8-bound Lck. ZAP-70 is then recruited to CD3ζ, and can also be phosphorylated by Lck. ZAP-70 then phosphorylates LAT, allowing for the recruitment of additional enzymes and adaptors and subsequent downstream events, principal amongst which are cytoskeletal changes, increases in intracellular calcium and the activation of ERK 1/2. Antigen recognition leads to enhanced internalization of the TCR–CD3 complex; interestingly, non-engaged TCR–CD3 complexes are also internalized at an increased rate. The factors that modulate the balance between sustained signalling and early TCR degradation remain ill-defined. It is clear that much remains to be discovered in this vital aspect of immune function; a complete understanding of TCR activation probably must await the development of new assays and technologies.

The AIDS pandemic, the increasing use of immunosuppressive agents in patients of autoimmune disease and in organ transplant recipients, and application of myeloablative therapeutic regimens in cancer patients, have all contributed to the rise in fungal infestation in humans. As Lionakis *et al.* (pp. 157–191) discuss, the development of murine models, as well as disease-association studies in humans have increased our understanding of innate and adaptive immune mechanisms that mediate protection against these pathogens. Though an estimated 5×10^6 fungal species are believed to exist, only a minor sub-population are known to infect humans; in immune compromised individuals, infections become life-threatening. Innate immune recognition of fungi occurs via a host of pattern-recognition receptors, including C-type lectin receptors (CLRs), TLRs, NOD1, NOD2, NLRP3, CD36, CD14, CR3 and the mannose receptor. Genetic disorders affecting CLR signalling preferentially result in susceptibility to fungal infection. The binding of fungi-derived β-glucan to the CLR Dectin-1 ultimately

leads to activation of the canonical NFκB pathway, as well as the activation of ERK and JNK. Both opsonised and unopsonised fungi can be killed by neutrophils. The precise role of neutrophil extra-cellular traps in protection awaits further definition. Several inherited disorders, caused either by 22q11.2 deletion, trisomy 21 or mutations in a spectrum of genes (such as *MALT1*, *BCL10*, *IL17F*, *IL17RA/RC*, *IL21R*) are associated with chronic mucocutaneous candidiasis. While live, attenuated vaccines and subunit vaccines have demonstrated efficacy in animal models, enhanced understanding of host–pathogen interaction will spur the development of novel preventive and curative intervention.

Retroviruses are often referred to a 'genome invaders'. The immune system is capable of responding to extracellular viral particles, to viruses that are detected within cells, as well as to integrated viral elements, as Cirion *et al.* (pp. 193–220) describe. Retroviral RNA serves as a ligand for TLR7 and TLR8; plasmacytoid DCs (pDCs), which produce type I interferons in response, can play significant roles in the activation of natural killer cells and T cells. However, some studies suggest that pDCs are unlikely to be present in adequate numbers at mucosal sites. Myeloid DCs, on the other hand, are constitutively present at mucosal sites, and also express TLR7. TLR7-mediated events have been shown to be essential in the control of murine leukemia virus infection. Cytosolic viral RNA is sensed by MDA5, PKR, RIG-I and OAS1–3; recognition of viral RNA which is produced subsequent to integration and transcription can also occur. Double-stranded DNA (dsDNA) products, arising subsequent to reverse-transcription, can lead to inflammasome activation, the secretion of IL-1β, and pyroptosis; such phenomena may contribute to the death of $CD4^+$ T cells during HIV infection. A prominent hallmark of mucosal infection in SIV models is an increase in pDCs numbers, and elevated levels of cytokines and chemokines. Subsequent to innate immune events upon HIV-1 infection, large-scale activation of $CD8^+$ T cells occurs, coinciding with a decline in viral titres; however, exhaustion of $CD8^+$ T cells is later observed. Interestingly, 'HIV controllers' demonstrate higher levels of fully differentiated $CD8^+$ T cells and can naturally control infection. Though $CD4^+$ T cells are targets of HIV, HIV-specific cytotoxic $CD4^+$ T cells are believed to contribute towards lowering levels of viremia. In most instances however, infection of T follicular helper (Tfh) cells sustains viral replication in the lymph node. Diminished and altered antibody responses, a consequence of affected Tfh function, can negatively affect antibody-dependent cell-mediated cytotoxicity and other effects frequently observed in 'HIV controllers'.

The liver seems ideally suited to detect microbes that gain access to the body via the oral route. The organ harbours a large complement of phagocytes, and contributes in no small measure to the generation of protective immunity, as Kubes *et al.* (pp. 247–277) discuss. The liver is primed to support anti-inflammatory outcomes, as portal blood can also carry non-pathogenic moieties, such as components of food; appropriate triggers can manifest in quick immune activation, however. It has become apparent that multiple immune cell types help maintain a fine balance between activation and tolerance in the liver, a balance that is critical for organismal health. Aberrant activation can cause tissue damage, while lack of appropriate responses is associated with inability to clear infection, and with cancer.

Flaviviruses cause a whole host of diseases across the globe. Ngono *et al.* (pp. 279–308) focus on infections cause by mosquito-borne dengue and zika viruses. In particular, dengue is a major public health issue, with multiple viral serotypes in circulation; 400 million new infections and about 20,000 deaths occur each year. While immunity to the dengue virus can be achieved, anti-viral antibody responses can also enhance viral infections in some instances. Dengue and zika viruses often co-circulate; a high degree of homology exists, with the result that T cell responses and antibodies often cross-react. Zika virus causes congenital zika syndrome, characterized by microcephaly and cerebral malformation. In adults, zika infection has been associated with Guillain-Barré syndrome, and the possibility that the virus can be sexually transmitted is a growing concern. A deeper appreciation of host responses would aid in the development of new therapeutics and vaccines.

The complement system, integral to innate immune defence, functions to neutralize pathogenic microbes. Many complement proteins serve as pathogens recognition motifs. For several years, its main roles appeared to be restricted to the opsonization and destruction of invading organisms. Complement deficiency results in greatly enhanced susceptibility to infection; alternatively, complement deficiency also leads to enhanced likelihood of systemic autoimmune disease, due to the integral role of the complement system in clearance of immune complexes. As West *et al.* (pp. 309–338) discuss, complement components, originally believed to be sourced from the liver, are now known to be made by a variety of cells, and autocrine functions in immune cells have been described. It is being increasingly revealed that the complement system plays significant roles in determining B and T cell responses. For example, in resting human CD4 T cells, intracellular cathepsin L cleaves C3 into bioactive C3a and C3b, mediating T cell survival via mTOR activation. C3a and C3b thus made can translocate to the cell surface, where interaction with respective receptors is believed to assist in the secretion of IFN-γ. Intracellular C5a–C5aR1 interaction in T cells increases the generation of ROS that can drive cellular activation. The 'complosome' also works to regulate metabolic cellular processes in T cells. Cross-talk with other innate immune sensors (such as the inflammasome) has also been described. Several issues remain unexplored, however. For example, the precise make-up and roles of the complosome in distinct T cell lineages remains unknown. Further, the sub-cellular location of complement components has also not been elucidated. Description of the role of intracellular complement in autoimmunity, diabetes and cancer should shed more light on these pathological states.

Immunological tolerance to self-moieties requires the destruction, editing, or silencing of self-reactive lymphocytes. Much information has been gathered about the mechanisms which prevent the activation of naive, autoreactive B cells. Post-activation, the somatic hypermutation of the B cell receptor presents a unique challenge to immune homeostasis, as it can potentially give rise to self-reactive B cells; while the processes that mitigate such outcomes are unclear to a large degree, Brink *et al.* (pp. 339–357) discuss what is currently known. There is

evidence to suggest self-reactive germimal centre B cells undergo apoptosis upon contact with antigen. Additionally, while RAG proteins are probably not expressed in germinal centre B cells (thus preventing the possibility of conventional receptor editing), autoreactive cells that arise due to somatic hypermutation may undergo further somatic hypermutation, a process that could rid the receptor of self-reactivity. While many mechanistic details await elucidation, what is clear is that the generation of autoreactive antibodies is not a general consequence of the formation of germinal centers; that said, it is also apparent that pathogenic self-reactive antibodies do arise. There is hope that emerging technologies and newer experimental models would expand understanding, leading to better therapeutics for autoantibody-mediated autoimmune pathologies.

In mammals, immunoglobulins of the IgA isotype are secreted by the intestinal mucosa. Deep sequencing technologies are being utilized to characterize antigenic specificities of IgA clonotypes as they relate to the modulation of the microbiome to promote mutualism, as Macpherson *et al.* (pp. 359–381) discuss. While somatic mutations that cause the emergence of diverse IgA clonotypes can proceed in the absence of high-affinity B cell receptor–antigen interaction, somatically mutated IgA are nevertheless believed to be essential for the maintenance of intestinal microbiota diversity. Emerging evidence suggests that IgA influences microbial metabolism and can work to dampen mucosal inflammatory responses. That said, there is need to elucidate the cumulative physiological impact of a wider spectrum of IgA clonotypes on microbial taxa. Such work will shed a critical light on the functioning of dominant immunoglobulin isotype.

IL-2 is central to the functioning of the adaptive immune system. Ross *et al.* (pp. 411–433) describe its known roles, and highlight the more enigmatic aspects of this pleiotropic cytokine. STAT5 appears to be important for IL-2 function, although mTOR- and PI3K-mediated signalling has also been described. IL-2 signalling, in addition to impacting T cell differentiation, also plays role in influencing metabolic pathways. The cytokine induces the phosphorylation of several proteins, while decreasing the phosphorylation of several others. Interestingly, IL-2 acts differently in different T cell subsets; in Tregs, it drives differentiation and homeostasis, while in effector T cells, it induces proliferation. Cellular responses to IL-2 are influenced by local concentrations of the cytokine, and gradients can be very steep; at least some IL-2 responses appear to be all-or-none, as opposed to being graded. It is increasingly appreciated that other metabolic signalling events can affect IL-2 signalling outcomes. For example, IL-2 can enhance the uptake of glucose and glutamine, in turn potentially enhancing O-GlcNAcylation of proteins on serine and threonine residues; O-GlcNacylation of threonine can block phosphorylation, affecting IL-2-mediated events. A deeper understanding of the pathways and factors that impact on IL-2 signalling in the context of specific T cell subsets is essential to fully comprehend the effects of the cytokine.

Extracellular vesicles (EVs), either pinched off directly from the plasma membrane or sourced from endosomes, are increasingly under study as agents of inter-cellular communication. Studies indicate that EV concentrations can reach up to 10^5/ml in human blood. The events that govern the formation of EVs or determine their molecular contents remain to be fully elucidated. EVs can demonstrate cell-specific targeting, and vesicle cargo can mediate complex down-stream events. Lindenbergh *et al.* (pp. 435–459) review what is currently known about the roles EVs, sourced from antigen presenting cells play in the triggering, expansion and down-regulation of adaptive immune responses. While DC- or B cell-derived EVs can interact with cells at distant sites, most EVs probably target cells nearby. Cargo composition of EVs released by dendritic cells is a function of DC activation status; accordingly, DC-derived EVs can have either inhibitory or stimulatory effects. Activation of DCs by LPS, or cognate interactions with CD4 cells, heighten EV release. CD86 and intercellular adhesion molecule 1 (ICAM-1) are found at higher concentrations in EVs derived from mature DCs, while EVs from immature DCs contain more MFG-E8. EVs can carry MHC Class I molecules, and EVs incubated with tumour-derived peptides can elicit CTL responses, particularly in the presence of bystander DCs. DCs presenting peptide-MHC Class I complexes transferred by EVs can prime CD8 T cells. EVs can also carry MHC Class II molecules, as well as costimulatory molecules. Injection of mice with such EVs results in the activation of primed CD4 T cells. DC-derived EVs can effectively initiate immune responses, and evidence exist that such events contribute to effective immunity. Whether DC-derived EVs can play a role in cancer immunotherapy is being considered. Activated DCs elicit EVs which have an enhanced capacity to induce anti-tumour immunity. Artificial EVs (comprising liposomes with peptide-MHC-I complexes, adhesion molecules and activation molecules) can trigger human antigen-specific CD8 T cells in the presence of bystander DCs. It is apparent that much remains unknown about EV-induced immune regulation.

Cellular functions are the consequence of the engagement or the suppression of metabolic pathways. Glycolysis and oxidative phosphorylation cooperate to supply the cell with ATP; glycolysis also provides intermediates for other metabolic pathways. Geltink *et al.* (pp. 461–488) focus on metabolic activity in naive and activated T cells. 'Tonic' signalling occurs as naive T cells circulate, engaging with self-MHC molecules loaded with self-peptides in interactions believed to be weak; cells import small amounts of glucose to sustain homeostatic proliferation, with IL-7 providing additional survival signals. Recent thymus-emigrant naive T cells are not as responsive to external stimuli as are circulating naive T cells. Lower mTORC1 and c-Myc levels are responsible for such a phenotype. In recent thymus-emigrant naive T cells, mTORC1 and c-Myc levels can be heightened by IL-2, sourced from T effector cells. In addition, sphingosine 1-phosphate signals also promote naive T cell survival. Driven by PI3K/AKT/mTOR signalling, activation of T cells augments global metabolism, while c-Myc drives the transcription of other essential genes. While the generation of reactive oxygen species is considered a vital step, given that it leads to the activation of nuclear factor of activated T cells (NFAT) and subsequent IL-2 secretion, cells appear to titrate the levels of ROS to achieve optimal activation. Cell division in T cells is asymmetric in terms of the distribution of cellular components. The presence of higher levels of activated mTORC1 in one daughter cell drives towards a T effector state characterised by high glycolysis, while the other daughter cell is fated to become a

long-lived memory cell. CD28 co-stimulation, critical for the prevention of anergy, also serves to enhance glycolytic metabolism, whereas ligation of PD-1 down-modulates glycolysis and T effector cell function. Subsequent to T cell stimulation, inhibition of phosphoinositide 3-kinase (PI3K) activity has been shown to drive Treg differentiation. PTEN is a negative regulator of PI3K signalling, and PTEN-knockout mice develop autoimmune lymphoproliferative disease. The absence of mTOR decreases cholesterol biosynthesis, and deletion of a transporter that mediates cholesterol efflux specifically in T cells leads to increased Treg numbers and suppressive activity. Tregs can exhibit metabolic flexibility, depending on particular tissue environments; Tregs that are found in visceral adipose tissue (VAT) acquire a specific phenotype. Interestingly, while in lean individuals such Tregs exhibit suppressive activity, obesity causes loss of suppressor function, and attended infiltration of T effector cells. While the development of check-point therapies and CAR-expressing T cells has advanced anti-cancer treatment options, enhanced understanding of why T cells in the core of the tumour become hyporesponsive would further this objective. A wider appreciation of the links between T cell function and metabolism will enable the development of powerful new therapeutics.

Between 10 billion and 100 billion cells are generated every day and an equal number die, and are efficiently disposed of by professional phagocytes in a non-inflammatory process known as efferocytosis. Additionally, infection with pathogens can induce necroptosis or pyroptosis, which constitute inflammatory forms of cell death. The processes and pathways involved in the clearance of cellular debris have been the focus of intense investigation, as Nagata (pp. 489–517) discusses; 'Find me' and 'Eat me' signals, expressed by dying cells, are critical to phagocytic recognition and engulfment. Aberrance in these events is believed to contribute to systemic autoinflammation. Apoptosis is mediated by specific caspases; more than 1300 substrates of these enzymes have been identified. The intrinsic apoptotic pathway is regulated by Bcl-2 family members (pro-apoptotic BH3-only members, pro-apoptotic effector molecules and the anti-apoptotic Bcl-2 family proteins), and is activated in response to developmental cues, depletion of critical growth factors, or the presence of a genotoxic agent. The extrinsic pathway is triggered by external ligands belonging to the TNF family (FasL, TNF-α, TRAIL). Phosphatidylserine exposure is essential for the phagocytic recognition of apoptotic cells. In healthy cells, P-type ATPases ('flippases') are responsible for keeping phosphatidylserine confined to the inner membrane. While cleavage by caspase 3 inactivates flippase activity, a 'scramblasé' is required to ensure adequate phosphatidylserine exposure. Milk fat globule EGF factor 8 (MFG-E8), which binds phosphatidylserine, acts as a bridge between the lipid and phagocytes to promote uptake. TIM4, expressed in macrophages found in the spleen, lymph nodes and fetal liver, serves as a receptor for phosphatidylserine which it binds via its immunoglobulin domain to aid efferocytosis. Inefficient efferocytosis results in cells undergoing secondary necrosis; while DNA is cleaved by various DNase enzymes, other remnants are taken up by scavenger receptors or via C1q-mediated uptake. Non-cleaved DNA, if it persists, can induce inflammatory outcomes upon engagement of TLR9 on dendritic cells and macrophages. Several diseases (for example, sepsis, systemic lupus erythematosus, cystic fibrosis, asthma) are characterized by abnormal efferocytosis. Further description of pathways driving this process would no doubt shed light on pathologies associated with these conditions.

Amongst opportunistic infections which occur in HIV-infected individuals, *Mycobacterium tuberculosis* (*M. tb*) is the most common; infection with *M. tb* is the leading cause of mortality in HIV patients. Esmail *et al.* pp. (603–638) discuss the biology and immunology of HIV–*M. tb* co-infection. HIV infection greatly increases the chances of contracting tuberculosis. Interestingly, the risk of active *M. tb* increases soon after HIV sero-conversion when CD4 can still be relatively high, as opposed to infections with *Pneumocystis jirovecii* or *Cryptococcus*, which require more advanced immune suppression. In co-infected individuals, as the extent of immune suppression increases with advancing HIV infection, the severity of *M. tb*-associated lung disease also increases. Lung infection in immune-competent patients results in the formation of granulomas, which are believed to be associated with decreased bacterial load and disease latency; HIV co-infection disrupts the formation of these structures. HIV co-infection also compromises the ability of neutrophils to fight *M. tb*. In patients with latent *M. tb*, even the early phases of HIV-1 infection are characterized by reduced levels of *M. tb*-specific $CD4^+$ T cells. *M. tb*-specific $CD4^+$T cells appear to synthesize lower levels of MIP1β (a ligand for CCR5 which antagonizes the binding of HIV) and exhibit higher expression of CCR5, making them preferential targets for HIV. That said, it is abundantly clear that T cells are critically required for protection against tuberculosis; Th1 cells and 'polyfunctional' T cells may all contribute, although controversies exist as to the roles of the latter.

The intracellular and extracellular milieu is constantly surveilled for the products of infection by pattern recognition receptors (PRRs). Chow *et al.* (pp. 667–694) review how the immune system discriminates between microbial nucleic acids and those of the vertebrate host; such work assumes importance in light of the fact that aberrant PRR activation has been associated with several immune disorders. Distinct families of PRRs are tasked to identify and neutralize a diversity of viral pathogens. PRR engagement results in a multitude of molecules that assist in host defence, including interferons, proinflammatory cytokines and chemokines. Viral RNA in the cytosol is sensed by retinoic acid-inducible gene I (RIG-I)-like receptors (RLRs), while viral RNA in the endosome is recognized by toll-like receptors (TLRs). The outcome is an amplification of the innate immune response, characterized by the induction of interferon-stimulated genes (ISGs), several of which encode proteins with antiviral effects; novel viral RNA sensors are being identified. A more comprehensive understanding of the basis of non-self nucleic acid recognition and subsequent downstream events will aid in the design of more efficient strategies for therapeutic intervention in both infectious disease and autoimmunity.

'Nanobodies' refer to the variable region of heavy chain-only antibodies derived from Camelidae. Ingram *et al.* (pp. 695–715) describe their properties and utility. Animals can be immunized and affinity-matured nanobodies isolated. High sequence homology to human V

regions is apparent, with the CDR3 loops being generally longer than those found in conventional antibodies, and nanobody affinities for antigen can be in the same range as conventional antibodies. While the cytoplasmic expression of traditional antibodies, as well as of scFvs, poses a challenge due to several reasons, nanobodies can serve stand-alone recognition units for use as intracellular probes; neither disulphide bonds nor glycosylation appear to be required for binding. A further advantage is that they demonstrate high solubility and are temperature stable. Being about a tenth the size of regular antibodies confers on nanobodies significant benefits. Since expression in cells can alter localization and/or function of targeted moieties, nanobodies can complement RNAi or gene-knockout technologies. While short circulatory half-life is a potential disadvantage, enhanced accessibility to tissues *in vivo* can heighten the sensitivity and resolution of imaging technologies. Their increasing use will no doubt lead to fresh insights into biological processes.

The term 'Inflammatory Bowel Disease' (IBD) covers within its ambit a wide array of intestinal disorders – Crohn's Disease (CD), Ulcerative Colitis (UC) and IBD Unclassified (IBDU) constitute the main phenotypes. Uhlig *et al.* (pp. 755–781) discuss current aspects of pathology and therapeutics. Environmental factors, the microbiome, as well as genetic and epigenetic factors all play a role in onset; incidence and prevalence appears to be on the rise. IBD is characterized by cycles of flares followed by periods of remission; acute episodes can be life-threatening, and lack of treatment can lead to cancer. Drug-mediated immune-suppression has been traditionally employed, and therapies that target inflammatory cytokines have been more recently used. Though effective in many cases, some patients are non-responsive to these treatments; it is increasingly believed that restoring microbial balance and epithelial barrier function is required to achieve long-term remission. That said, the first imperative is to more fully understand the immunobiology of the disorder.

That, in addition to the immune system, the nervous system also works to stave off the deleterious effects of injury and infection, is becoming increasingly apparent. Pavlov *et al.* (pp. 783–812) describe aspects of this exciting interface. It appears likely that the nervous system and the immune system present a joint front in the face of physiological insult. Inflammation in the periphery can affect brain function; neurological complications in conditions such as sepsis and systemic lupus erythematosus are prime examples. The brain appears to integrate communication between the nervous and immune systems. Sensory neurons can detect microbial moieties (via TLRs), as well as inflammatory cytokines (via specific receptors). Contrarily, immune cells have been shown to express receptors (such as for muscarinic and nicotinic acetylcholine) involved in neural communication, and can also make several neurotransmitters. Insights into the mechanisms of cross-talk between the neurological and immune systems raise the possibility of therapeutic intervention. For example, stimulation of the vagus nerve appears to provide benefit in sepsis, IBD, arthritis, and in autoimmune disease. Electric neuromodulation has been shown to benefit patients of Crohn's disease and rheumatoid arthritis. The field of bioelectronic medicine is set for a major advance in the coming years.

Given the complexity of the immune system as well as inherent genetic variability, predicting how it will respond in a given situation represents a formidable challenge. Villani *et al.* (pp. 813–842) primarily focus on work aimed at building predictive models for two critical aspects of T cell activation: MHC-peptide interaction and MHC-TCR binding. It is becoming clear that the immune system works to protect organismal health and integrity by relying on complex, interconnected networks in which feed-back and feed-forward pathways form intergral parts. Several non-immune cell types are also targets, as well as active participants, in this effort. While breakdown in effective immunity can result in lethal infection, breakdown in the mechanisms that function to restore immune homeostasis can result in run-away inflammation, autoimmunity or debilitating allergy. In the unwell, it is clear that the development of effective and safe immunotherapeutic modalities requires an expanded, system-wide understanding of immune networks and pathways. Single-cell profiling is expected to provide interesting insights into healthy and diseases states, and also possibly reveal the existence of novel differentiation states. Going forward, establishing rules of cellular activation that are generally applicable versus those that are individual-specific would become increasingly important.

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