Immunity to viruses

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The analysis of the innate and adaptive immune response to viruses has provided fundamental insight into the functioning of the immune system. Early studies on the host response to virus infection were instrumental in establishing the concept of immunological tolerance (1). Similarly, the realization that T lymphocytes are 'restricted' in their recognition of antigens by gene products encoded within the major histocompatibility complex (MHC) locus came from the analysis of T-lymphocyte recognition of virus-infected cells (2). Likewise, important initial insights into antigen processing and presentation came from the analysis of viruses and virus-infected cells (3, 4).

Until recently, it was convenient to view immunity to infectious agents like viruses as a separate branch of immunology distinct from immunity to tumors, self-molecules (antigens), or allergens. As demonstrated in many of the articles in this volume of *Immunological Reviews*, the mechanisms underlying the induction and regulation of the innate and adaptive immune response to viruses represent the same processes controlling immunity to tumor antigens, allergens, and self-constituents. Thus, the results summarized in these review articles and the implications of these findings are applicable not only to those of us who study immunity to viruses but also to the immunology community at large.

In selecting the topics for review in this volume of *Immunological Reviews*, we were first and foremost limited by space. Consequently, many important contributors to the field of viral immunology (indeed several topics) are not represented in this volume. Our selection of topics and authors was biased towards emerging areas, such as the application of systems biology approaches to viral pathogenesis and immunity, the contribution of inflammatory and stress responses to the induction of Innate and adaptive immune responses, and the impact of the microbiome on immunity to virus infection. We also considered it relevant to include reviews focused on well defined areas where recent findings have resulted in potential paradigm shifts in our understanding of topics such as B-lymphocyte or T-lymphocyte responses to virus infection. This volume of *Immunological Reviews* is also somewhat weighted towards analyses of the immune response to respiratory viruses. With the recent episodic infections with the severe acute respiratory syndrome (SARS)-like coronavirus and the outbreak of human infections with the avian influenza A H7N9 virus, respiratory viruses such as these organisms are recognized as major human pathogens with the potential for pandemic spread. Therefore, this class of viruses is a focus of immunological research.

The reviews in this volume can be grouped according to the following scheme: (i) molecules and cells regulating the induction of the innate and adaptive response, (ii) expression of immune effector activity, (iii) regulation of the antiviral immune response, and (iv) systems analysis of the host response to infection and vaccination (Fig. 1).

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Induction of innate and adaptive immune responses

The initiation of the immune response to an invading microorganism like a virus requires that the host sense the organism and its constituents [e.g. uncapped viral RNA (5)] and/or cellular stress and consequent metabolic changes and cellular damage resulting from infection. This initial response to infection is carried out primarily by germline-encoded pattern recognition receptors (PRRs) (5, 6). Five types of PRRs have been identified. These include C–type lectin receptors (CLRs) and Toll-like receptors (TLRs) localized to the cell surface or within endosomes and intracellular retinoic acid inducible gene–I (RIG-I)-like receptors (RLRs), nucleotide oligomerization and binding domain (NOD)–like receptors (NLRs), and the Pyrin-HIN domain (PYHIN) receptors (5, 7, 8). Each of these receptor types has multiple members, and individual members of a receptor type variously recognize pathogen-associated products or damage-associated molecular patterns, such as reactive oxygen species, adenosine triphosphate (ATP), or apoptotic/necrotic cells (9).

The role of sensors such as TLRs and RLRs in virus infection is well established (5, 8). By contrast, the extent of the contribution of NLRs in the recognition of virus and virus-infected cells has only been appreciated more recently (10). NLRs are a large receptor family including at least 20 members. NLRs play a dominant role in inflammasome activation resulting in the Caspase-1-dependent maturation and release from cells of the pro–inflammatory mediators interleukin-1 (IL-1) and IL-18. However, not all NLRs are pro-inflammatory. Engagement of certain members of this receptor family can downregulate pro–inflammatory signals generated by other PRR types (11). In addition, several NLRs have been reported to regulate antigen presentation events associated with the MHC class I and II presentation pathways (12, 13). In their review of the role of NLRs in antiviral immunity, Lupfer and Kanneganti (14) examine the role of specific NLRs in inflammasome activation and regulation during virus infection and the contribution of other NLRs to the regulation of inflammation and viral antigen presentation during virus infection.

One of the critical consequences of the engagement of certain PRR types, e.g. TLRs and RLRs by virus infection, is the induction of the interferon (IFN) response. Type I IFNs were initially identified and named based on their antiviral properties. However, in addition to upregulating genes that inhibit virus replication, this class of cytokines has been appreciated to play an important role in orchestrating the adaptive immune response to virus infection. Recently, a new family of antiviral cytokines, the type III IFN family, has been identified. The type III IFNs (also known as IFN 1, 2, 3 or IL-29, IL-28A, IL-28B, respectively) appeared to activate the same antiviral pathways and transcriptional factors, e.g. IFN-stimulated gene factor 3 (ISGF3), as the type I IFNs. However, the type III IFNs have little structural homology with their type I counterparts and engage a distinct heterodimeric receptor, which includes the IL-10R2 chain (15). In their article, Durbin and coworkers (16) summarize the current understanding of antiviral signaling by type I and type III IFNs, with particular emphasis on the induction of these cytokines and the expression of antiviral activity of these two cytokine families at mucosal surfaces, notably the respiratory tract and gut following infection with influenza A virus (IAV), respiratory syncytial virus (RSV), or rotavirus (RV). They also summarize our current understanding of the immunomodulatory effects of these cytokines on the induction of the adaptive immune response through their effect on specific cell types, for example natural killer (NK) cells and dendritic cells (DCs) (17), and the distinct signal transduction events associated with immune modulation by IFN.

Another important consequence of PRR engagement in response to microbial infection is the induction of the autophagy response. Autophagy is a catabolic recycling pathway induced by stress, e.g. the endoplasmic reticulum stress response (19). Microbial infection promotes autophagy by a variety of mechanisms (19). In their review on the impact of autophagy on

CD8$^+$ T-cell-mediated antiviral immunity, Perot and colleagues (20) review the complex interplay between viruses and three pathways of response to virus infection, that is autophagy, the innate immune response, and the adaptive immune response. In this article, the authors describe the subcellular constituents making up the autophagy response and strategies that viruses employ to either enhance or inhibit autophagy and the consequences of alterations in autophagy on innate and adaptive immune response induction. Of particular note is the recent evidence on the contribution of autophagy to viral antigen processing and presentation to CD8$^+$ T cells. They further extend this analysis to evaluate the impact of autophagy on T-cell differentiation in the thymus in the process of lymphocyte activation in the periphery.

DCs are cellular sentinels that link the innate and adaptive immune systems. As a cell type, they are well endowed with a range of PRR sensors for both pathogen-associated ligands and damage-associated ligands generated during virus infection. This sentinel role is particularly crucial at body surfaces such as the skin, gastrointestinal tract, and lungs, which are the major sites of pathogenic microorganism entry into the body. Although distinct from macrophages, DCs are not a uniform population but exist as distinct subsets with different properties/functions, in different activation states dependent upon the site of DC localization, i.e. in secondary lymphoid tissue, deep in body tissues, or at mucosal surfaces.

Neyt and Lambrecht (21) review the lung DCs, their diversity, function in the steady-state and following lung inflammation, as well as activation in response to respiratory virus infection. This report examines the consequences of direct activation of DCs by virus infection as well as indirect or *trans* activation of DCs by products released by airway epithelial cells, themselves responding to engagement of their PRRs by virus or cellular stress. For example, IL-1 produced by respiratory epithelial cells following PRR engagement acts in an autocrine fashion to release DC-attracting chemokines as well as granulocyte-macrophage colony-stimulating factor (GM-CSF) to support DC recruitment and viability and factors involved in epithelial regeneration (IL-33). DC migration from the lungs to the draining lymph nodes is an essential step in the initiation of the antiviral T-cell response. Type I IFNs are the most potent inducers of DC maturation resulting in DC migration (22). This report also reviews current findings on the role of individual DC subsets in orchestrating different aspects of the adaptive immune response, including the dominant role of the CD8a/CD 103$^+$ DC family in cross-presenting viral pathogen to naive CD8$^+$ T cells and the role of C–type lectins (most notably DNGR-1) in capturing viral antigen delivered by dying epithelial cells (23). This report points to the 'division of labor' among DC subsets in the induction of antiviral effector responses and in the control of local inflammation at the site of infection, i.e. the respiratory tract.

Expression of immune effector activity

NK cells serve as major innate immune effector cells functioning in the control of virus infection (24). They simultaneously display germline-encoded activating and inhibitory receptors in various combinations on a given cell. The inhibitory receptors are sensitive to the level of expression of MHC class I molecules on cell surfaces, so-called 'missing self' (25). NK cells also display PRRs, which respond to pathogen-derived and/or damage-induced ligands.

NK cells have been implicated in control of infection with the number of viruses both in human and in experimental models. One human virus infection where NK cells have been implicated to play a role both in control of virus replication as well as in the development and control of tissue damageis chronic infection with hepatitis C virus (HCV). Approximately 150–200 million people worldwide are estimated to have chronic HCV

infection. HCV persists in up to 80% of infected individuals with only a minority of individuals clearing infection without therapeutic intervention. The ability of this virus to persist in such a large fraction of infected individuals suggests that it is capable of dysregulating the host innate and adaptive immune response to allow its persistence in the liver. Although modified IFN-based regimens have been the standard of treatment for HCV for more than a decade, success rates vary substantially depending on the genotype of HCV infecting the patient. Understanding the mechanisms that regulate immunity against this virus in the liver and in particular the contribution of NK cells to resistance and recovery from infection is essential the development of improved therapies and ultimate cures.

In their article, Golden-Mason and Rosen (26) review basic aspects of the biology of NK cells including the process of NK cell activation and the NK cell molecules that control the activation state of NK cells. They then go on to focus on the role and properties of NK cells during the acute and chronic stages of HCV infection, the impact of treatment on NK cell responses with emphasis on the properties of NK cells specifically localized to the liver and the effect of HCV infection on the properties and function of liver NK cells. They conclude with an analysis of NK cells as regulators of liver fibrosis, crosstalk between NK cells and DCs, and speculate on the potential role of NK cell memory (27) following infection and the prospects for the development of vaccines targeted to NK cells.

In her review of B-cell responses to virus infection, Baumgarth (28) takes us to the interface between the innate and the adaptive immune response to virus. Using IAV as a model system, she explores the development and role of polyreactive natural antibody B-cell responses and the role and function of germinal center B-cell responses in infection. Polyreactive natural antibodies are largely of the immunoglobulin M (IgM) class and are generated independent of antigen challenge (29) by a distinct class of B lymphocytes, B-1 (CD5$^+$ B-1a and CD5-B-1b) B cells. The immunoglobulin receptor on B-1 cells is diverse but does not normally undergo Ig class switch. B-1 cells and their natural antibody products were initially believed to be self-reactive and potentially capable of producing autoimmunity. However, it is becoming increasingly clear that they can bind pathogen-associated antigens. B-1 lymphocytes qualify as innate immune cells much like NKT cells, which also rearrange their receptor genes, but unlike NKT cells exhibit considerable diversity in V gene usage.

The polyreactive nature of these antibodies is due to the pentameric structure of the IgM immunoglobulin. The development, function, and regulation of the B-1 lymphocytes and their natural antibody products are discussed in the context of their role in IAV infection (28). The impact of B-1 lymphocytes on influenza infection discussed in relation to the response of conventional extrafollicular and germinal center B-2 B lymphocytes. The article concludes with evidence suggesting that repertoire diversity and broadly cross-reactive polyreactive B-cell responses, as exhibited by B-1 and extrafollicular B-2 responses, may be more important than B-cell affinity maturation (in the germinal center) for effective B-cell immunity to pathogens like IAV, which can undergo rapid antigenic variation.

The *sine qua non* of the adaptive immune response is the apparent exquisite specificity of individual B and T lymphocytes. However as the aforementioned description of B-1 B cells and polyreactive natural antibodies suggest, this apparent high degree of specificity was not always observed. In the case of T lymphocytes, there were multiple early examples of T-cell cross-reactivity for apparently unrelated antigens (30). Perhaps this was best exemplified from the early studies of Welsh and coworkers (31, 32) demonstrating cross-reactive recognition of heterologous viruses by memory CD8$^+$ T cells. Su and Davis (33) review the topic of T-cell receptor (TCR) cross-reactivity in the development of CD4$^+$ memory T-cell responses in both the mouse and human. This detailed review covers topics ranging from the

pre-immune T-cell repertoire and the structural basis of T-cell cross-reactivity for seemingly unrelated viruses to the functional consequences of TCR cross-reactivity and the contribution of the microbiome to regulating the T-cell repertoire and TCR cross-reactivity on the development on human disease and responsiveness to vaccination.

Moseman and McGavern (34) continue with the theme of the consequences of TCR engagement of peptide/MHC (pMHC) complexes with specific emphasis on the formation and *in vivo* significance of immunological synapse formation. They review the evidence for and against the need for the formation of a stable mature immunological synapse to transduce signaling events and to express effector activity in activated CD4$^+$ and CD8$^+$ effector T cells. They employ intravital two-photon laser scanning microscopy (35) to obtain real-time information on the interaction of cytotoxic T-lymphocyte TCRs with pMHC displayed on infected cells in the model of lymphocytic choriomeningitis infection in the central nervous system. Their most recent evidence suggests that effective interactions between T cells and virus-infected cell targets, resulting in virus clearance or in some instances immune-mediated injury, can be either stable (with mature immunological synapse formation) or transient [with 'kinaspe' formation (36)] depending on the target cell type and the extent of pMHC formation.

Molecules that express costimulatory or co-inhibitory activity following engagement of their respective ligands play a central role in all aspects the host's adaptive immune response to virus infection. Engagement of costimulatory receptors is necessary for the activation naive antiviral T cells. Costimulatory and co-inhibitory receptors and their ligands can modulate the differentiation of activated T cells into effector or memory cells at critical steps during the evolution of the of the antiviral T-cell response, thereby controlling the magnitude of the T-cell response at the site of infection and thereby diminishing the potential for immune-mediated tissue injury. Wortzman and co-authors (37) review the role of tumor necrosis factor receptor (TNFR) family members in antiviral immunity, emphasizing five TNFR members that primarily serve a prosurvival role in antiviral CD8$^+$ T cells but can in some instances limit the antiviral T-cell response, i.e. exhibit co-inhibitory activity when the receptor is engaged. They also discuss the potential role of TNFR ligands as vaccine adjuvants and TNFR family members as targets for therapeutic intervention in chronic viral infections.

The topic of CD4$^+$ T-cell differentiation and regulation of development of specific CD4$^+$ T-cell subsets has been a topic explored previously in *Immunological Reviews*. The past decade has seen a substantial increase in the number of defined effector CD4$^+$ T-cell subsets from two to at least six. In their article, Strutt *et al.* (38) undertake the challenging task of providing an integrated view of the synergistic role of several of these effector CD4$^+$ T-cell subsets and the corresponding memory T-cell populations in response to experimental IAV infection. They reprise their earlier studies on the synergy between cytolytic effector CD4$^+$ T cells and conventional T-helper 1 (Th1) effector CD4$^+$ T cells in virus clearance and recovery from IAV infection. They review the evidence for compartmentalization of function of various effector CD4$^+$ T-cell subsets and the importance of anatomical localization of responding CD4$^+$ T cells and the expression of effector activity. They also present the evidence for regulation of effector functions in lymphoid and nonlymphoid compartments by transcription factors.

While CD4$^+$ (and CD8$^+$) T cells can be categorized into subsets based on their functional properties and effector activities, memory T cells can be divided into subsets based on their recirculation and homing properties. For more than a decade, memory T cells were subdivided into T-effector memory (Tem) and T central memory (Tcm) cells. Tem cells primarily circulate through nonlymphoid tissues, while Tcm circulate through and home to

secondary lymphoid organs. More recently, analyses have identified a third memory T-cell subset, the T tissue-resident memory (Trm) cells (39). Trm cells primarily localize to and are retained in peripheral tissues. The localization and retention at these sites require expression of specific chemoattractant and homing receptors. Shin and Iwasaki (40) categorize peripheral tissues based on the accessibility of these tissues in the resting or inflamed state to effector T cells or the several subsets of memory T cells. They review the mechanisms regulating the migration of memory T cells in the steady state and in response to inflammation in particular virus infections. They describe the factors that control the generation of Trm cells and the properties that distinguish Trm from the Tcm and Tem cell subsets. Finally, they explore the potential role of Trm cells in vaccination against pathogens that invade the body through peripheral tissues.

Regulation of immune effector activity during virus infection

Because of the potential to produce serious injury as a byproduct of recognition of an invading microorganism, the innate and adaptive immune systems have evolved multiple failsafe mechanisms to control the magnitude and quality of the immune response. One of the most important cell types involved in the control of the responses is the regulatory T cell. Veiga-Parga and co-authors (41) focus on the CD4$^+$ regulatory T cells (Tregs) expressing the transcription factor forkhead box protein 3 (Foxp3) and the contribution of this regulatory T-cell subset to antiviral immunity. They describe the mechanisms by which viruses induce responses from natural (thymus-derived) Tregs as well as inducible Tregs, which are derived from naive virus-specific primary CD4$^+$ T cells. They discuss the instances where Tregs limit antiviral T-cell responses or control excess immune-mediated inflammation. They explore in detail the potential role of Tregs in chronic infection with human immunodeficiency virus (HIV) and HCV and the potential therapeutic possibilities of harnessing Treg responses to manage the outcome of virus infection, particularly in the context of chronic inflammation and injury associated with persistent virus infection.

The Miller laboratory has carried out seminal studies on the link between virus infection antiviral immunity and the development of autoimmune responses (42). Herein, Getts *et al.* (43) discuss 'traditional' mechanisms by which virus infection results in local or systemic autoimmune diseases, e.g. autoreactive T-cell responses induced by viral molecular mimicry, as well as more controversial mechanisms of induction of autoimmune responses, such as virus-induced decoy mechanisms to dysregulate immune recognition events resulting in autoimmune responses.

Myeloid derived suppressor cells (MDSCs) are immature myeloid lineage cells that were initially detected in the circulation and in the microenvironment of human tumors. At least two 'subsets' of MDSCs have been identified displaying properties of either immature granulocytes or immature monocyte/macrophage lineage cells. As their name suggests, they are potent suppressors of antitumor immune responses. In recent years, evidence has emerged that MDSCs may play a role in immune evasion by viruses, particularly viruses that can produce persistent infection. In their review, Goh *et al.* (44) discuss the mechanisms involved in the generation and accumulation and survival of MDSCs during virus infection and the critical targets of MDSC action including T cells, NK cells, and antigen-presenting cells. They go on to catalog the list of viral infections in which the activity of MDSCs has been reported and then explore MDSCs as targets for therapeutic intervention in the treatment of chronic virus infections.

In considering regulation of the immune response, one of the most exciting areas to have recently emerged is the evidence linking the magnitude, quality, and duration of the immune response to the host commensal flora, i.e. the microbiota. While this topic has been the

subject of recent reviews in *Immunological Reviews*, Wilks and colleagues (45) focus their article on the impact of commensal bacteria on the host response to virus infection, as exemplified by the impact all of antibiotic treatment on IAV pathogenesis and the host adaptive response to the virus (46, 47). We are still in the early days in our understanding of the role of commensal microorganisms in controlling innate and adaptive immune responses to viruses, but as indicated elsewhere in this volume (33), data are emerging to suggest both subtle and potentially profound effects of microflora on the antiviral immune response and outcome of virus infection.

Systems approaches to vaccination, viral pathogenesis, and the host response

The development of high throughput screening technology as well as advances in computer software and hardware have opened up new and exciting possibilities for the analysis of the host response to virus infection as well as vaccine development. Graham (48) reviews the past successes and failures in the development of effective viral vaccines, focusing on HIV vaccine development and trials. He discusses vaccination strategies in the context of augmenting cytolytic neutralizing antibodies and/or CD8$^+$ T-cell responses and the necessity and feasibility of vaccination leading to sterilizing immunity. He goes on to describe the impact of new technologies, notably high throughput sequencing and the application of structural biology approaches to antigen design on vaccine development. He concludes with a realistic assessment of the prospects for effective vaccine development against newly emerging viruses and viruses with the potential for producing chronic persistent infection.

The systems biology approach to data acquisition is hypothesis neutral, that is, it relies on the application of one or more profiling technologies, for example genomics, transcriptomics, and proteiomics, to broadly evaluate the host response to an immunological stimulus both over time, e.g. following infection or vaccination, and over space, e.g. sampling at different sites in the body. Data obtained from this molecular profiling can be used to formulate hypotheses for traditional research analyses. It can also be used in an iterative fashion to expand or narrow the data acquisition platform. In their report, Pulendran and co-authors (49) discuss the systems approach to the analysis of human vaccination against yellow fever virus and IAV with the ultimate aim of establishing the molecular profile of a successful immune response to vaccination. Studies such as these have begun to reunite the fields of vaccinology and basic immunology. The systems approach to vaccination evaluation has begun to identify the importance of stress sensors in establishing an effective vaccination strategy and in the future may provide a molecular signature of a successful response to vaccination as well as the parameters that could be associated with an adverse reaction to vaccine.

Menachery and Baric (50) take this strategy one step further and review their systems biology approach to viral pathogenesis in the analysis of the host response to coronavirus and IAV infection. They demonstrate how this hypothesis-neutral approach can lead to testable hypotheses, i.e. identification of targets amenable to the hypothesis-driven reductionist approach. They also showcase the application of the 'collaborative cross' strategy to identify novel gene targets that regulate various aspects of the host response to these viral pathogens in the new learning model.

Concluding remarks

In this compendium, we showcase aspects of the host innate and adaptive immune response to viruses. We hope that these thoughtful and thorough reviews will help drive lines of investigation in the area of viral immunology. We also hope that those of you whose

research is in other areas of immunology will likewise obtain insights that will help move forward your own research programs.

Acknowledgments

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Fig. 1. Immunity to viruses
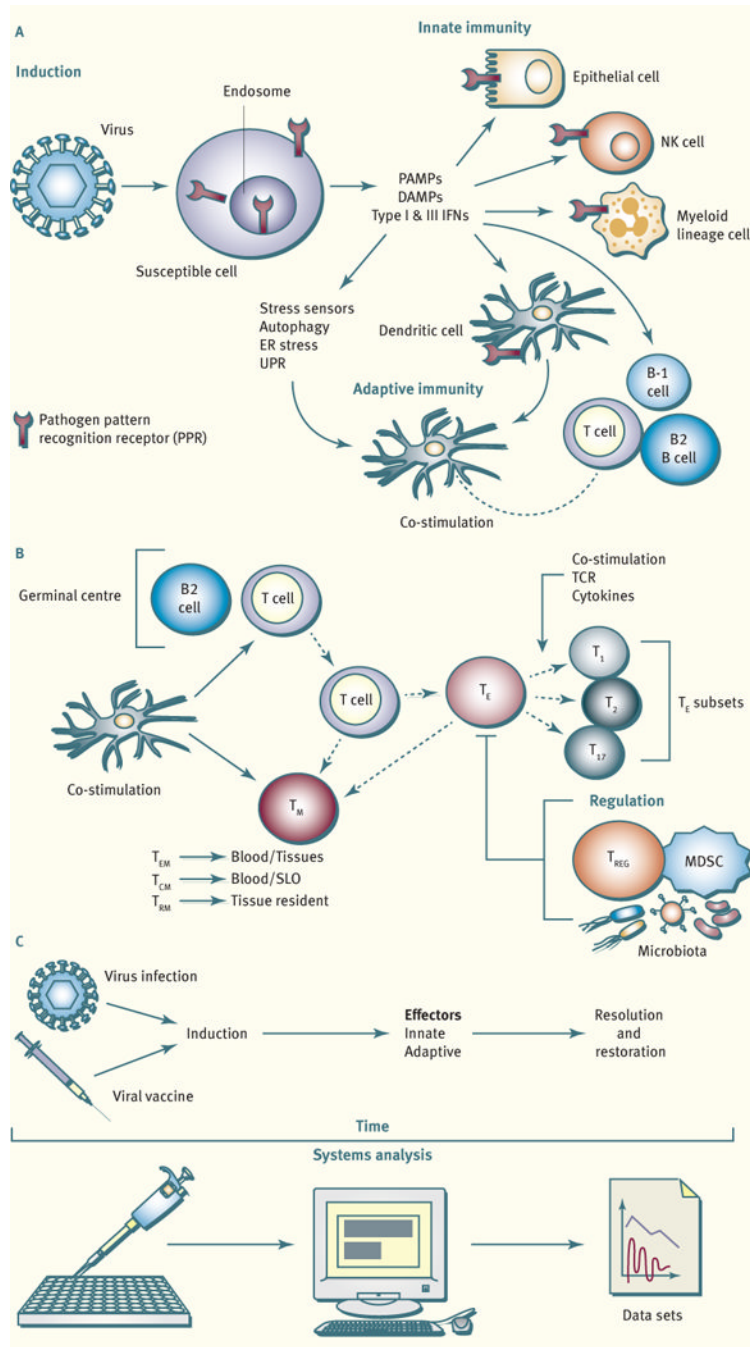(A) Host response to virus infection. (B) Expression and regulation of effector activity. (C) Global analysis.