Immunity and immunopathology to viruses: what decides the outcome?

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Abstract | Many viruses infect humans and most are controlled satisfactorily by the immune system with limited damage to host tissues. Some viruses, however, do cause overt damage to the host, either in isolated cases or as a reaction that commonly occurs after infection. The outcome is influenced by properties of the infecting virus, the circumstances of infection and several factors controlled by the host. In this Review, we focus on host factors that influence the outcome of viral infection, including genetic susceptibility, the age of the host when infected, the dose and route of infection, the induction of anti-inflammatory cells and proteins, as well as the presence of concurrent infections and past exposure to cross-reactive agents.

Humans may be infected by and suffer clinical consequences from numerous different viruses, and in most instances the infection is resolved with or without tissue damage. Reinfection is usually subclinical, and for many viruses we have effective vaccines; classic examples include measles, mumps, rubella, rotavirus and varicella zoster viruses. Other viruses, such as HIV, hepatitis C virus (HCV), hepatitis B virus (HBV) and some herpesviruses, can cause substantial tissue damage in some or all individuals they infect, and lesions can become chronic. These viruses usually have one or more properties that allow them to diminish the efficacy of host adaptive or innate immunity, and we lack effective vaccines against most of these agents. Infection with viruses such as influenza virus and respiratory syncytial virus (RSV) has a variable outcome. Most individuals may suffer mild or subclinical infection, but others experience severe disease that can be lethal. Of particular interest are agents such as West Nile virus, dengue virus and poliovirus that can cause severe disease, but only in a small minority of infected people. Finally some viruses, such as coxsackie B virus, human T lymphotropic virus, Epstein–Barr virus (EBV) and possibly rubella virus, are thought to act as triggering agents for autoimmune diseases and cancer in genetically susceptible individuals. The topic of virus-associated complications has been reviewed by others[1,2] and will not be discussed here.

In this Review, we discuss our current understanding of the circumstances of infection and host-controlled factors that could explain why an infection can be resolved with minimal impact or cause substantial tissue damage. Understanding such issues could prove to be useful in the future for the control and perhaps prevention of tissue-damaging virus infection.

Tissue damage caused by the immune system

Almost all virus infections cause the recruitment and activation of inflammatory cell types — particularly macrophages and, in some infections, neutrophils — that in turn release a range of molecules that induce tissue damage or malfunction. These include cytotoxic cytokines, cationic proteins, lipid mediators, metalloproteinases and components of the oxygen burst. The reactive oxygen species that accumulate in the mitochondria may further contribute to tissue damage[3]. Both innate and adaptive immune signalling events are involved in mediating tissue damage.

Contribution by innate immune responses. Invading viruses and their replicative intermediates can be recognized by several innate immune receptors expressed either at the host cell surface or within cells. Many types of innate immune receptor can participate in the immune response but, in virus infections, the most studied are the Toll-like receptors (TLRs), retinoic acid-inducible gene I (RIG-I; also known as DDX58) and NOD-like receptors (NLRs). Virus infections usually activate the endosomal TLRs (TLR3, TLR7, TLR8 and TLR9) that recognize viral nucleic acids and double-stranded RNA intermediates[4]. The cytoplasmic RIG-I-like receptors recognize viral genomic RNA or RNA encoded by genomic DNA, whereas the NLRs recognize viral DNA genomes (reviewed in REF. 5). In general, activation of many of these receptors causes the production of pro-inflammatory cytokines and interferons (IFNs), as well as signals that recruit and activate cells involved in inflammation and the induction of adaptive immunity. The pattern of innate

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immune events induced after the entry of virus may dictate the outcome of infection. Many viruses that persist trigger innate cells such as dendritic cells (DCs), natural killer (NK) cells and macrophages to produce anti-inflammatory molecules such as interleukin-10 (IL-10) and transforming growth factor-β (TGFβ). For example, DCs from lymphocytic choriomeningitis virus (LCMV)-infected mice produce high levels of IL-10 (REF. 6), and IL-10 is produced by monocytes from individuals infected with HIV, HCV or HBV[7–9]. Following RSV infection, the interaction between the virus and lung plasmacytoid DCs (pDCs) is crucial, as the removal of pDCs before infection favours an immunopathological reaction in the lungs[10]. A damaging response to a virus infection is more likely to occur with viruses that can interfere with one or more innate defences. Some examples of viruses that have this effect and the innate defence mechanism that is diminished are listed in TABLE 1.

Contribution by adaptive immune responses. Once adaptive immune effector cells are generated, these can contribute to tissue damage. T cells, for example, can directly destroy virus-infected cells or release cytokines, such as tumour necrosis factor (TNF), that damage cells. With some non-cytopathic virus infections, such as HCV and HBV, destruction of infected cells by CD8^{+} effector T cells is the main cause of damage to the liver[11,12] (BOX 1; FIG. 1). Responses to infected cells by different types of CD4^{+} T cell orchestrate a tissue-damaging inflammatory reaction and these become chronic against persistent viruses. Most often, the cell subsets involved are T helper 1 (T_H1) cells, but T_H17 cells may contribute to inflammatory responses during HIV, HCV and influenza virus infections[13–15]. In such T_H17 cell-driven responses, neutrophils are recruited and become a major source of tissue-damaging molecules. T_H2 cells are rarely associated with inflammatory responses during viral infections, but a T_H2 cell response can occur during severe lung responses to RSV infection[16].

Antibody responses to viruses may also contribute to tissue damage. This occurs when antibody binds to an infected cell, activates complement and causes an inflammatory reaction. Alternatively, antibody-mediated inflammatory reactions involve toxicity following engagement of IgG with Fc receptors on inflammatory cells, which causes inflammatory mediator release[17], or following deposition of viral antigen–antibody complexes in capillary beds, leading to activation of the complement cascade. Lesions formed by immune complex deposition can occur when viruses persist and poorly neutralizing IgG is produced; lesions include nephritis, polyarteritis and arthritis. Immune complex lesions were first reported in LCMV infection but have also been reported in chronic HCV and HBV infection, as well as in idiotypic IgA nephropathy associated with HIV infection[18–21]. Viruses such as RSV express antigens that may induce an IgE response and type I hypersensitivity might partially account for lung lesions in some children infected with RSV[22].

Despite these possible occurrences, tissue damage is modest in most cases of viral infections; however, the level of tissue damage can vary between individuals infected with the same virus. In the following section, we describe the host responses that function to minimize tissue damage.

Host factors that limit tissue damage

The host can use many countermeasures to limit tissue damage after virus infection. These tissue-protective events are more effective against some viruses and some circumstances of infection than others, accounting for the different pattern of response observed among individuals. The countermeasures include the production of cytokines such as IL-10 and TGFβ that have anti-inflammatory activity, other host-derived anti-inflammatory mediators such as resolvins and galectins, the activity of cell subsets that inhibit other cells from mediating inflammatory events, as well as the induction of molecules on effector cells that result in the loss of effector functions (FIG. 2).

Anti-inflammatory cytokines. The two best-known cytokines that inhibit inflammatory reactions are IL-10 and TGFβ. Many cell types can produce IL-10, including subsets of activated DCs, macrophages (when infected with some viruses), activated regulatory T (T_{Reg}) cells, B cells and some subsets of NK cells following stimulation with TLR ligands[23]. Although some viruses, such as EBV and cytomegalovirus (CMV), produce an IL-10-like molecule that functions *in vitro* in a similar manner to host IL-10, it is still not clear if this viral IL-10 has any role during viral infections *in vivo*[24,25]. Host-derived IL-10 can block pro-inflammatory cytokine and chemokine production and MHC class II expression, and it can also interfere with many signalling pathways that result in pro-inflammatory cytokine production. For example, nuclear factor-κB (NF-κB) signalling is inhibited by IL-10-mediated induction of p50 and p105 NF-κB subunits, one of which (p50) binds to the stimulatory subunit p65, sequestering it in the cytoplasm and making it unavailable for binding to the promoters of IL-6 and CC-chemokine ligand 3 (also known as MIP1α) for their transcription (reviewed in REF. 26). IL-10 also suppresses type I IFN-induced tyrosine phosphorylation of signal transducer and activator of transcription 1 (STAT1) and also induces the expression of suppressor of cytokine signalling 3 (SOCS3) by macrophages and neutrophils, which impairs their inflammatory activity.

The extent of IL-10 production during an infection could influence the amount of tissue damage that occurs. Thus, if the IL-10 response is absent, owing to genetic mutation, or is artificially suppressed by antibodies specific for IL-10 or its receptor, inflammatory reactions to infectious agents may be exaggerated. For example, mice lacking an IL-10 response develop more severe inflammatory reactions to ocular infection with herpes simplex virus (HSV) than do normal controls[27]. IL-10 may be of particular importance to constrain the severity of inflammatory reactions caused by chronic infections, and its anti-inflammatory function has been shown during infection with viruses such as HCV and HIV[9,28,29].

Plasmacytoid DC
A dendritic cell (DC) subset with a morphology that resembles that of a plasmablast. Plasmacytoid DCs produce large amounts of type I interferons in response to viral infection.

Resolvins
Resolution-phase interaction products that are made by the host from eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) and that have anti-inflammatory properties.

Galectins
A family of lectin proteins that bind a wide variety of glycoproteins and glycolipids containing β-galactosides through their carbohydrate-recognition domain. They have extracellular and intracellular functions, including the regulation of apoptosis, RAS signalling, cell adhesion and angiogenesis.

Regulatory T (T_{Reg}) cells
A subset of T cells that control the activity of effector T cells under inflammatory or steady state conditions.

Table 1 | **Virus and host features that favour tissue damage**

Feature	Virus	Effect on host	Refs
Viral evasion strategies			
Interference with innate immune responses	HCV	Blocks RIG-I pathway by degrading IPS1	117
	Influenza A virus	NS1 protein inhibits RIG-I by direct interaction	
	Paramyxovirus	V protein inhibits RIG-I by interacting with MDA5	
	HIV and human herpesvirus	Inhibit IRF3	
	Hantaan virus, CCHFV and Borna disease virus	Viral RNA is undetectable by PRRs owing to removal of 5′ triphosphates	
Interference with antigen processing and presentation	HSV	ICP47 blocks TAP-mediated peptide transport	118
	CMV	US3 inhibits tapasin; US6 blocks TAP-mediated peptide transport; gp40 retains MHC class I molecules in ER; pp65 prevents activation of IRF3	119,120
	EBV	EBNA1 inhibits the proteasome; IL-10 homologue downregulates MHC class II expression	121,122
	HIV	Nef protein inhibits cell surface expression of CD4 and MHC class I molecules	123
Infidel replication machinery and variants	HCV, HIV and influenza virus	Escape removal by antibodies and CTLs and emergence of variants	124
Viral homologues of host regulatory proteins	CMV	CMV IL-10-like protein competes with host IL-10 for binding IL-10 receptor	25
	EBV	IL-10 homologue; EBI3 protein related to p40 subunit of IL-23 and IL-27	122,125
Dose of infection*			
High	HBV	Immunopathology of the liver	92
	Influenza virus	Inadequate CD8^{+} T cell response	91
	LCMV	Induces CTL exhaustion	126
Low	HBV	Immunopathology of the liver	92
	LCMV	Choriomeningitis	98
Route or location of infection			
Intratracheal	Reovirus	Virus-specific IgA and double-positive (CD4^{+}CD8^{+}) T cell responses	127
Oral versus footpad	Reovirus	Restricted CD8^{+} T cell repertoire induced by oral infection	128
Intracranial versus intravenous	LCMV	CD8^{+} T cell-mediated lethal choriomeningitis occurs on intracranial infection and viral persistence occurs on intravenous infection	98
Host genetic susceptibility			
Defective type I and II IFNs	Poliovirus	Increased susceptibility to paralysis	71
	HSV and VZV	Increased susceptibility to encephalitis	74,112
TLR3 polymorphism or deficiency	HSV-1 and VZV	Increased encephalitis	74,112
	WNV	Decreased encephalitis	94
	Influenza virus	Decreased acute pneumonia	129
TLR2 polymorphism	HSV-2	Increased genital lesions and viral shedding	130
HLA-DR7 versus HLA-DR2	HBV	Chronic carrier versus viral clearance	131
CCR5Δ32bp	HIV	Resistance to macrophage-infecting virus	109
HLA-B35 versus HLA-B57	HIV	Rapid versus delayed progression to AIDS	132
HLA complex P5 rs2395029	HIV	TT versus GG genotype: high versus lower viral load at set point	133
HLA-C 5′ region 9264942	HIV	TT versus CC genotype: high versus lower viral load at set point	133
HLA-DQB1*031 and HLA-DRB1*11	HCV	Spontaneous resolution	134
IL-28B polymorphism	HCV	CC genotype associated with spontaneous resolution and response to treatment, TT genotype associated with persistent infection and poor response to treatment	135,136
MXA, *OAS1* and *PKR* polymorphisms	HCV	TT genotype at −88 in *MXA*, GG genotype in 3′ UTR of *OAS1* and CT genotype at −168 of *PKR* give rise to self-limiting disease	135,136

Table 1 (cont.) | **Virus and host features that favour tissue damage**

Feature	Virus	Effect on host	Refs
Age when infected			
Young	Influenza virus and RSV	Increased susceptibility to infection (in RSV because of inadequate type 1 immune response)	138,139
Adult	EBV, VZV, measles virus and mumps virus	Increased susceptibility to infection	72,101
Old	VZV, CMV, RSV and influenza virus	Increased susceptibility to infection	81,138
Prior infection			
EBV	Influenza virus	Increased susceptibility to infection as immune responses to M protein cross-react with BMLF1 of EBV	102
Flaviviruses	Dengue virus	DHF or DSS	100

CCHFV, Crimean-Congo haemorrhagic fever virus; CCR5, CC-chemokine receptor 5; CMV, choriomeningitis virus; CTL, cytotoxic T lymphocyte; DHF, dengue haemorrhagic fever; DSS, dengue shock syndrome; EBI3, EBV-induced gene 3; EBNA1, Epstein–Barr virus nuclear antigen 1; EBV, Epstein–Barr virus; ER, endoplasmic reticulum; HBV, hepatitis B virus; HCV, hepatitis C virus; HSV, herpes simplex virus; ICP47, infected cell protein 47; IFN, interferon; IL, interleukin; IPS1, *IFNB*-promoter stimulator 1; IRF3, interferon-regulatory factor 3; LCMV, lymphocytic choriomeningitis virus; Nef, negative factor; MDA5, melanoma differentiation-associated gene 5; *MXA*, myxoma resistance protein A; *OAS1*, 2′5′ oligoadenylate synthetase 1; *PKR*; protein kinase R; PRR, pattern recognition receptor; RIG-I, retinoic acid-inducible gene I; RSV, respiratory syncytial virus; TAP, transporter associated with antigen processing; TLR, Toll-like receptor; UTR, untranslated region; VZV, varicella zoster virus; WNV, West Nile virus. *Dose of infection with lentiviruses[88], simian immunodeficiency virus[89] and HCV[12] has no effect on the host response.

Recently, IL-10 production by virus-specific effector T cells during the acute response to influenza virus was shown to be responsible for minimizing the severity of pulmonary lesions in mice[30]. The responding CD8^{+} T cells showed plasticity and gained the ability to produce IL-10 in addition to their main effector product, IFNγ. Inhibiting the response to IL-10 with antibody specific for the IL-10 receptor resulted in more severe and sometimes fatal virus-induced lung damage. IL-10 production by effector CD8^{+} T cells and the IL-10-induced suppression of IL-2 production by these cells were also shown in HIV-infected patients[31]. Suppression of the effector T cell IL-10 response by lethal strains of influenza virus, such as the 1918 H1N1 strain and the H5N1 strain, is thought to contribute to their virulence[32]. In some instances excessive IL-10 production during a virus infection may inhibit a protective effector T cell response and favour viral persistence[6]. This can happen in some circumstances with LCMV infection and may also occur during HIV infection[6,9].

The TGFβ superfamily of cytokines has a similar anti-inflammatory role to IL-10, although the effects of TGFβ are more complex. These cytokines have a wide range of activities that include both anti-inflammatory and pro-inflammatory effects with the outcome depending on the concentration of TGFβ available and some other factors[33]. Moreover, TGFβ superfamily members exist in a latent, inactive form and must be cleaved before they can bind to receptors and mediate their effects on cells. Nevertheless, the extent of TGFβ production during virus infection could influence whether the response becomes overtly tissue damaging. Accordingly, TGFβ inhibits several functions of T cells, including proliferation, differentiation into effector T cells and some effector functions such as cytotoxicity[34]. The inflammatory activities of CD8^{+} T cells, T_H1 cells and T_H17 cells, as well as the production of inflammatory products by recruited cells, are all inhibited by TGFβ[34].

Most of our knowledge of the role of TGFβ in microbial pathogenesis concerns non-viral pathogens[35,36]. However, some viruses do cause an increase in TGFβ levels, and other viruses express proteins that can cleave and activate TGFβ. For example, influenza virus neuraminidase can activate TGFβ, and the extent to which this happens could influence virulence[37]. Among the viruses that cause increased TGFβ production are chronic infections by HBV and HCV. A nonstructural protein of HCV (NS4) was shown to be responsible for TGFβ induction and it seems that the magnitude of the TGFβ response, with IL-10 production, could determine if HCV infection is effectively cleared or becomes chronic[14]. Acute infection with reovirus may also activate TGFβ signalling to an extent that correlates with damage to the central nervous system[38]. Of note, virus-specific CD8^{+} T cells isolated from HCV-infected individuals produce TGFβ that suppresses virus-specific T cell responses[39]. Moreover, blockade of TGFβ enhanced the *in vitro* activity of T cells[39]. Furthermore, a recent report attributed an intrinsic role of TGFβ signalling in effector T cells to explain their diminished survival and effector functions during chronic LCMV infection[40].

IL-10 and TGFβ are not the only cytokines that can limit damage caused by inflammatory reactions. Recently, for example, IL-17 — a cytokine that is normally associated with the promotion of tissue damage — was shown to have an anti-inflammatory role by suppressing T_H1 cell-mediated inflammatory effects[41]. The suppressive effect of IL-17 was noted initially with autoimmune lesions but was recently also observed during infection with Theiler's murine encephalomyelitis virus in mice[42].

Other anti-inflammatory molecules. Several other natural host products can also participate in the control and resolution of inflammatory reactions (FIG. 3). These include the galectins, resolvins and protectins. These molecules contribute to the resolution of inflammatory lesions in several non-infection-related lesions[43]. Members of the

Box 1 | **Viruses that persist and cause chronic disease**

Several human viral infections — for example HIV, hepatitis B virus and hepatitis C virus (HCV) — become persistent, and some can cause severe chronic disease that is usually the consequence of an immune reaction to the virus. Many herpesviruses persist but rarely cause chronic disease in normal (immunocompetent) hosts. During HIV infection, the virus is never eliminated from the body, as it integrates into the genome of infected host cells and has several immune evasion strategies. These include antigenic variability, the structure of its envelope, which makes it refractory to neutralizing effect of antibodies, replication in and destruction of CD4+ T cells, induction of immune imbalance and induction of expression of inhibitory receptors by CD8+ T cells, making the cells functionally ineffective.

   HCV infection causes chronic lesions in ~85% of infected individuals, but the remaining ~15% control the infection and clear virus from the liver. HCV is a non-cytopathic infection that replicates for several weeks before an adaptive immune response occurs. Viral clearance is mediated by T cells, and this causes hepatocyte destruction and mild hepatitis. The virus has several means of inhibiting innate immune mechanisms and the effects of these may relate to whether control of the virus or chronic infection ultimately occurs. The virus-encoded attenuators of the innate immune response include inhibiting type I interferon (IFN) responses at several levels, raising the activation threshold of natural killer (NK) cell activation and having negative effects on dendritic cell maturation and function. Protective immunity is associated with the induction of IFNγ-producing CD8+ T cells and high numbers of T helper 1 cells. Individuals that develop chronic disease instead mount a response comprising interleukin-10 (IL-10)-producing CD8+ and CD4+ T cells and sometimes forkhead box P3 (FOXP3)+ regulatory T cells. However, it is not clear what accounts for the different outcome of HCV infection. It has been suggested that dose of exposure, polymorphism of genes affecting NK cell activation and concurrent disease or infections (for example, co-infection of HIV and HCV results in more severe hepatitis). The role of innate and adaptive events that affect HCV pathogenesis has been recently reviewed elsewhere[12].

galectin family might also help to constrain inflammatory reactions[43]. Galectin 9, for example, binds to the T cell immunoglobulin domain and mucin domain protein 3 (TIM3; also known as HAVCR2) on activated effector T cells and causes apoptosis, and at the same time it expands the T_{Reg} cell response[44–46]; both effects minimize tissue damage. It is possible that variations in galectin concentrations between individuals could explain why the outcome in some individuals is rapid and protective but in others it is prolonged and causes tissue damage. Currently, there is no evidence for this hypothesis; however, galectin levels are different between HIV- and HCV-infected individuals and controls, and in HCV infection galectin levels may correlate with viral loads[47,48].

T_{Reg} cells. Another mechanism of counteracting excessive tissue damage following virus infection is the induction, activation or expansion of several types of T_{Reg} cell, the main activity of which is to inhibit the function of other cell types. The best-studied T_{Reg} cells are CD4+ T cells that express the transcription factor forkhead box P3 (FOXP3)[49]. Such T_{Reg} cells could influence the outcome of infection, particularly those that are chronic in nature[50]. In model systems in which the activity of T_{Reg} cells can be inhibited, tissue-damaging immunopathological reactions to some viruses are increased. This was observed with the HSV ocular immunopathology model in mice[51]. Similar tissue-protective effects of T_{Reg} cells were noted in a Friend retrovirus model, as well as in mouse models of RSV and West Nile virus[52,53]. In the HSV ocular immunopathology model, recent observations showed the therapeutic value of increasing the proportion of FOXP3+ T_{Reg} cells to limit virus-induced immunopathological reactions[54,55]. This was achieved by administering reagents, such as galectin 9 and the fungal metabolite FTY720, that could cause some conventional CD4+ T cells to convert *in vivo* into FOXP3+

CD4+ T cells that have regulatory functions[45,55]. In several chronic human virus infections, T_{Reg} cells are thought to influence the extent of tissue damage, but this view remains debatable and is difficult to evaluate in natural disease situations[56]. Some of the most convincing evidence that T_{Reg} cells are beneficial in a human chronic viral infection came from observations of the disease outcome in patients accidentally infected with HCV. In this example, it was shown that a favourable outcome was more likely to occur in those individuals that made the highest IL-10-producing T_{Reg} cell responses[57].

The role of inhibitory receptors. An additional mechanism that could affect the pattern of events that follow virus infection is the signalling of inhibitory receptors on effector cells of both innate and adaptive immune systems. Such events may favour tissue damage over infection control. Several negative signalling systems that affect innate immune responses to virus infections have been noted, and many of these function by terminating NF-κB signalling, which curtails pro-inflammatory cytokine and chemokine production[58] (BOX 2).

   The protective function of effector T cells may also be compromised if they express inhibitory receptors and engage their ligands. The circumstances that result in upregulation of inhibitory receptors by effector T cells is not fully understood at a mechanistic level, but the effect usually becomes evident during chronic infections, especially those that involve high levels of persistent antigen[59]. Some of the well-characterized receptors that can be induced in chronic infection include programmed cell death 1 (PD1) and the IL-10 receptor. These molecules are expressed at higher levels by CD8+ T cells during chronic infection with LCMV in mice[6,60]. Their engagement with their respective ligands impairs effector T cell function, resulting in a so-called exhaustion phenotype. This exhaustion phenotype for effector T cells has since been observed in other

Protectins
A family of compounds that are derived from DHA and that are characterized by a conjugated triene-containing structure. They have been shown to regulate the influx of neutrophils at inflammatory sites.

Exhaustion
Impaired ability of effector T cells to carry out their functions such as cytotoxicity and cytokine secretion owing to chronic stimulation by antigen.
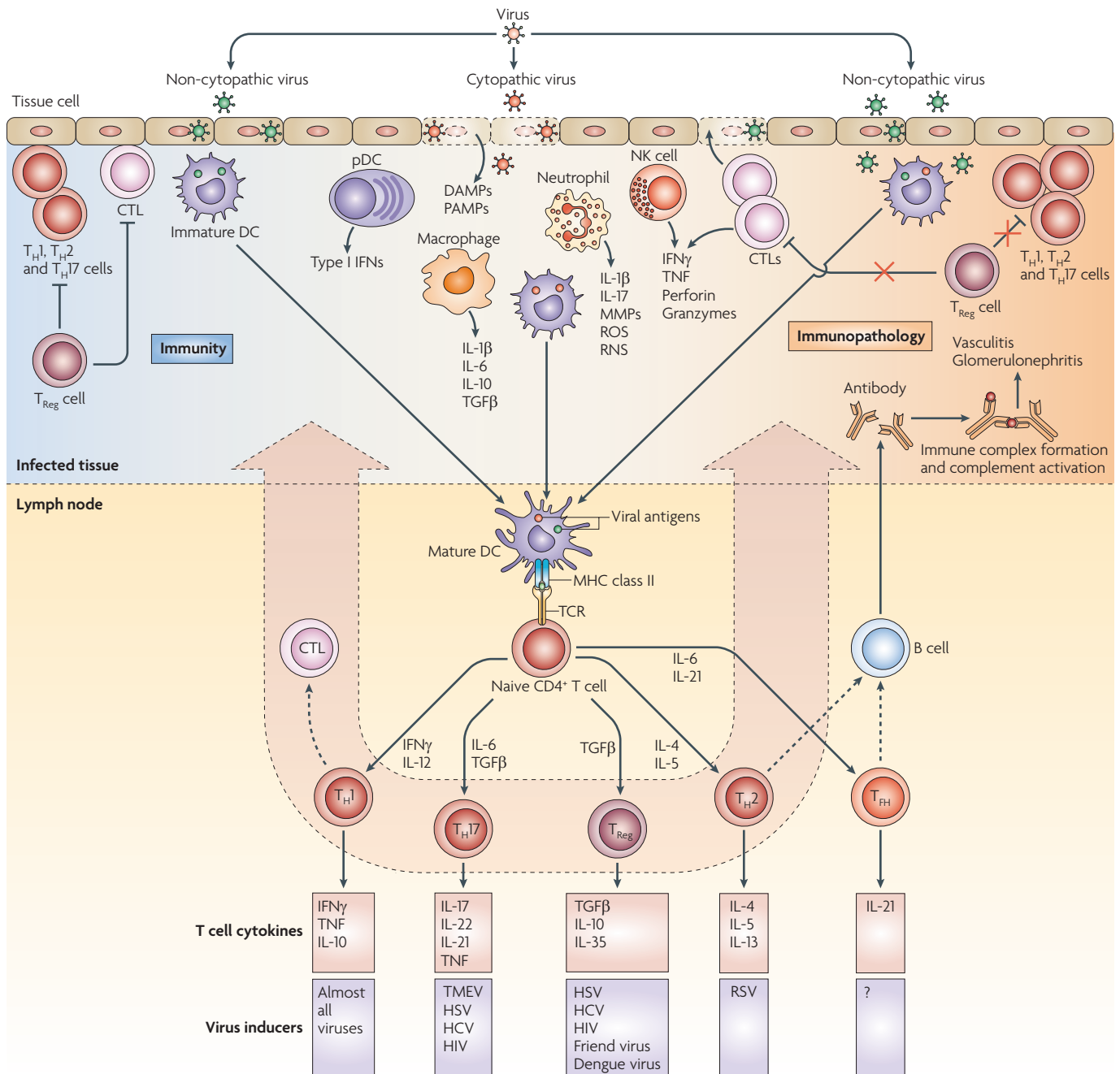
Figure 1 | **Immunity or immunopathology following viral infection.** Following entry into host cells, viruses (cytopathic or non-cytopathic) replicate at the site of infection. Cytopathic viruses kill infected cells, causing the release of cellular contents, including proteases and lysosomal enzymes, which digest the extracellular matrix and create an inflammatory milieu. Neutrophils that are rapidly recruited to the site of infection release inflammatory mediators. Innate cells recognize viral replication intermediates and secrete pro-inflammatory cytokines, which, in addition to helping to clear the virus, contribute to tissue damage. Viral antigens are taken up by antigen-presenting cells and carried to local draining lymph nodes. Depending on the cytokine milieu created in the draining lymph node, different types of T helper (T_H) cell responses are induced. Primed CD8+ cytotoxic T lymphocytes (CTLs) migrate to the site of infection and kill virally infected cells, thereby contributing to tissue damage. After migrating to the site of infection, T_H cells also contribute to the tissue damage. In conditions in which the control of aggressive T_H cells and CTLs by regulatory T (T_{Reg}) cells is impaired and other inhibitory pathways fail to curtail them, tissue damage is the main consequence of viral infection. T_H cells also provide help to B cells to secrete antibodies, which form immune complexes that are deposited in certain tissues such as the glomeruli of the kidneys and blood vessels to cause immune complex-mediated disease. DAMP, danger-associated molecular pattern; DC, dendritic cell; HBV, hepatitis B virus; HCV, hepatitis C virus; HSV, herpes simplex virus; IFN, interferon; IL, interleukin; MMP, matrix metalloproteinase; NK, natural killer; PAMP, pathogen-associated molecular pattern; pDC, plasmacytoid DC; RNS, reactive nitrogen species; ROS, reactive oxygen species; RSV, respiratory syncytial virus; TCR, T cell receptor; T_{FH}, T follicular helper; TGFβ, transforming growth factor-β; TMEV, Theiler's murine encephalomyelitis virus; TNF, tumour necrosis factor.

chronic infections, including HIV, HCV and HBV[61–63]. Some recent studies have suggested the existence of a correlation between the PD1–PD1 ligand 1 (PDL1) pathway and the production of IL-10. Thus, triggering of PD1 by PDL1 induced high levels of IL-10 production in monocytes that in turn inhibited the function of CD4+ T cells[64]. The IL-10-mediated inhibition of CD4+ T cell effector function was also shown in chronic LCMV infection in mice[6]. Exhausted T cells may express additional inhibitory receptors that include lymphocyte activation gene 3 (LAG3) and TIM3, with distribution varying in different locations[59]. Ligation of inhibitory receptors on exhausted T cells diminishes their protective function, allowing viruses to persist and cause more tissue damage. In fact, the TNF-producing ability of exhausted T cells that contributes to tissue damage

is one of the last functions to wane[59]. It is not clear how infection causes inhibitory receptor upregulation but in some instances a viral component has been implicated (for example, the HCV core protein) and in other cases virus-induced IFNs[63,65] or TLR ligands expressed by viruses are thought to have a role[66].

The discovery of the exhaustion phenomenon provides an enticing opportunity for the development of new approaches for improving immunity and controlling the severity of chronic viral infections. Accordingly, blockade of the signals that are responsible for the exhausted state can result in partial recovery of immune function and more effective infection control[6,60]. Initial observations focused on blockade of PD1 or PDL1, as well as the IL-10 receptor, using monoclonal antibodies, but blockade of several inhibitory signals was even more efficacious than blockade of a single component[67,68]. Thus, inhibition of either the PD1–PDL1 interaction and the IL-10 receptor or the PD1–PDL1 interaction and LAG3 provided the best approach to achieve immune recovery and viral control after chronic LCMV infection in mice. Furthermore, when both blockade of the exhaustion pathways and therapeutic vaccinations were carried out, control of chronic LCMV infection was greater than either approach alone[69,70]. It is likely, therefore, that similar strategies might prove to be useful for the control of human chronic infections.
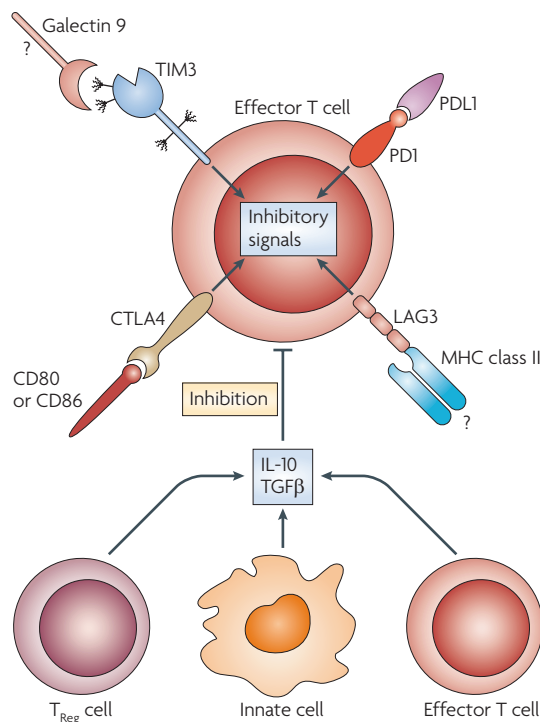
Factors that favour tissue damage

In this Review, we explore the question of why virus infection has varied outcomes in different individuals infected with the same virus. This issue is particularly difficult to address in the context of sporadic diseases that cause overt disease in only a small minority of infected persons. The classic example of this is paralytic polio, which affects less than 1% of individuals infected with poliovirus[71]. Reasons for susceptibility to poliovirus-associated disease remain unexplained but one favoured hypothesis is that the involvement of the central nervous system (CNS) is associated with a defect in type I IFN production, allowing robust poliovirus replication in the periphery and spread of the virus to the CNS[71]. Another example is herpes simplex encephalitis that occurs in adults. This is a rare, often lethal, debilitating disease caused by infection with HSV-1 (REF. 72). The disease usually occurs following reactivation of the host's resident latent virus, although primary infection can occasionally result in encephalitis and is a common outcome in seronegative neonates infected with HSV-2. Lesions of herpes simplex encephalitis in adults are, in part, immune mediated, but why they only occur in an unfortunate few is not known. Primary genetic susceptibility factors have not been implicated nor has the emergence of a neurotropic mutant, although recently a minority of cases of herpes simplex encephalitis in children were associated with polymorphism in the genes encoding TLR3 or UNC93B (which is involved in TLR signalling)[73,74]. In the following section we describe the situations that favour a tissue-damaging response over immune control (TABLE 1).

Figure 2 | **Inhibitory mechanisms to limit tissue damage caused by T cells.** Effector T cells upregulate inhibitory receptors such as programmed cell death 1 (PD1), T cell immunoglobulin domain and mucin domain protein 3 (TIM3), lymphocyte activation gene 3 (LAG3) and cytotoxic T lymphocyte antigen 4 (CTLA4) (and others such as adenosine receptors (not shown)) on their surface. Ligation of these receptors with PDL1, galectin 9, MHC class II molecules and CD80 or CD86, respectively, delivers inhibitory signals to the effector T cells and controls their inflammatory activity and subsequent tissue damage. In addition, activated regulatory T (T$_{Reg}$) cells, specialized innate cells or highly polarized effector T cells that can produce anti-inflammatory cytokines inhibit effector T cell responses. Inadequate control exerted by these pathways under some circumstances therefore results in uncontrolled T cell activation and proliferation causing excessive tissue damage. Question marks indicate interactions for which extensive *in vivo* studies have not been carried out. IL-10; interleukin-10; TGFβ, transforming growth factor-β.

a

Pro-inflammatory mechanisms

- **Cytokines and chemokines:** IL-2, IFNs, TNF, IL-1β, IL-6, IL-8, IL-12, IL-17, CCL2, CCL3 and CXCL2
- **Chemical mediators:** prostaglandins, histamines and cyclooxygenases
- **Reactive species:** reactive oxygen species and reactive nitrogen species
- **Proteinases:** matrix metalloproteinases

Anti-inflammatory mechanisms

- **T$_{Reg}$ cells**
- **Cytokines:** IL-10, TGFβ and IL-35
- **Chemical mediators:** resolvins, protectins, galectin 1 and galectin 9
- **Inhibitory receptors:** PD1, LAG3, TIM3 and CTLA4
- **Innate immune regulatory proteins:** TLR signal inhibitors: A20, IRAKM, SOCS1 and SOCS3 RLR regulators: RNF125, ubiquitin ligase, DUBA, NLRX1 NLR inhibitors: p202

b

Pro-inflammatory mechanisms

Anti-inflammatory mechanisms

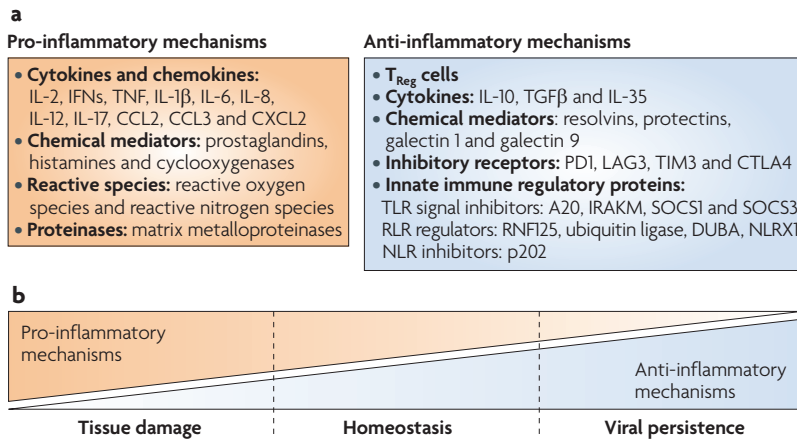| Tissue damage | Homeostasis | Viral persistence |

Figure 3 | **Balance between pro-inflammatory and anti-inflammatory mechanisms may decide the outcome of viral infection. a** | Pro-inflammatory and anti-inflammatory mechanisms induced after viral infection. **b** | The balance between immunity and immunopathology following viral infection might depend on the levels of anti-inflammatory and pro-inflammatory mechanisms. A balanced combination of pro-inflammatory and anti-inflammatory mechanisms would facilitate viral clearance and immunity to reinfection, with minimal damage to host tissues. An excess of pro-inflammatory mechanisms would ensure viral clearance but causes tissue damage. If anti-inflammatory mechanisms outweigh pro-inflammatory mechanisms, the pathogen could persist in the host as a subclinical infection, an opportunist or a tissue-damaging agent. CCL2, CC-chemokine ligand 2; CTLA4, cytotoxic T lymphocyte antigen 4; CXCL2, CXC-chemokine ligand 2; DUBA, deubiquitinase enzyme A; IFN, interferon; IL, interleukin; IRAKM, IL-1R-associated kinase M; LAG3, lymphocyte activation gene 3; NLRX1, NOD-like receptor X1; PD1, programmed cell death 1; RNF125, ring finger containing domain 125; RLR, RIG-I-like receptor; SOCS, suppressor of cytokine signalling; TGFβ, transforming growth factor-β; TIM3, T cell immunoglobulin domain and mucin domain protein 3; TLR, Toll-like receptor; TNF, tumour necrosis factor; T$_{Reg}$, regulatory T.

Latent infection
A dormant infection with a microorganism that persists in the body for a long period of time, but it can be reactivated under certain conditions, such as immunosuppression.

Shingles
A viral disease characterized by painful, blistering skin rashes due to infection or recurrence of infection with varicella zoster virus.

Age of infection. Whether a virus causes severe tissue damage often depends on the age at which infection occurs. For example, intrauterine infections may result in severe tissue damage, as happens following rubella virus and CMV infections in humans[75]. In general, it is the young and the elderly who suffer the most severe consequences of infection, as shown by increased morbidity and mortality among these age groups following infection with seasonal influenza virus[76]. Increased susceptibility of the young, especially neonates, has been attributed to immature responsiveness of the immune system, particularly components of innate immunity. For example, RSV is usually the first pathogen that a human infant encounters and clinical signs of RSV infection are common by 2–3 months of age[77]. Premature infants are particularly prone to develop severe lesions in the respiratory tract following RSV infection and these account for many of the 3–5% of childhood RSV infections that require hospitalization[77,78]. This high susceptibility of infants to RSV-induced immunopathology is mainly explained by an inadequate type I IFN response together with a failure to activate subsets of DCs that induce CD8+ T cell- and T$_H$1 cell-mediated protective responses[79]. Instead, the DCs that are stimulated tend to produce IL-10 and TGFβ and induce the generation of FOXP3+ T$_{Reg}$ cells[80]. Studies of RSV infection using animal model systems indicate that the main mediators of the lung pathology are T cells, but there is still debate as to which subsets are primarily involved. Some studies indicate a pathological role for TNF-producing CD8+ T cells, whereas other studies advocate that lesions are associated with T$_H$2 cell-dominated responses[16] (reviewed in REF. 78). Because childhood infection with RSV is a notable health problem, against which there is no effective vaccine, understanding at a mechanistic level why some individuals develop severe lesions to RSV is an important issue.

Aged individuals may also suffer more problems than younger individuals following primary or secondary infection with some viruses. For example, re-exposure of aged individuals to RSV can cause lesions similar to those that occur in infants[81]. In addition, aged individuals may develop lesions following reactivation of latent infections that had been successfully controlled by their immune system for decades. The best example of this is shingles, which is characterized by painful inflammatory skin lesions that occur at sites innervated by a sensory ganglion in which varicella zoster virus has been reactivated from latency[82]. It is not clear why this happens in only a few of the many ganglia that contain latent virus. It is possible that reactivation of latent virus occurs often but is successfully controlled by T cell immunity[83]. Presumably this T cell activity can fail at some sites but not others; further study is required to understand how this happens.

Understanding senescence of the immune system is an active area of research and the topic has been covered in excellent reviews[84,85]. Studies, mainly done in mice, have revealed that ageing has a greater effect on primary than on memory immune responses[84]. The T and B cells from aged individuals respond less well to antigens and are compromised in their ability to carry out effector functions compared with responses in young individuals. Moreover, naive T cells from aged compared with young animals undergo less homeostatic proliferation, probably because of competition with memory T cells for growth factors and anatomical space[84]. An additional effect observed during senescence is that the breadth of the T cell repertoire is reduced, perhaps because the thymus has involuted[84]. Indeed, compared with young individuals, aged individuals often have increased numbers of CD8+ T cells that recognize latent viral infections, particularly CMV infections — an effect known as memory inflation[86]. These CMV-specific CD8+ T cells can account for 50% or more of the total CD8+ memory T cell population. The space such cells occupy could diminish the number of lymphocytes available to react to pathogens, perhaps explaining why infections such as influenza virus are more severe in the elderly.

Dose and route of infection. As can readily be shown in experimental systems, the dose and route of transmitted virus can markedly influence the outcome of a virus infection. Minimal doses may be controlled subclinically by innate defences and may be insufficient to induce adaptive immune responses. Massive doses can overwhelm immune defences and cause severe disease and rapid death, in some instances by direct

Box 2 | Regulators of innate immune cells

After recognizing pathogen-associated molecular patterns (PAMPs) through their innate receptors (such as Toll-like receptors (TLRs), RIG-I-like receptors (RLRs) and NOD-like receptors (NLRs)), innate immune cells become activated and produce numerous inflammatory cytokines, including type I interferons, tumour necrosis factor (TNF), interleukin-6 (IL-6), IL-1β and some chemokines. Some of these molecules recruit other inflammatory cells such as neutrophils, which promote tissue damage. However, the host has evolved mechanisms to counter-regulate some or all of these pathways. Some of the important molecules and pathways include A20 deubiquitinase, IL-1R-associated kinase M (IRAKM), Toll-interacting proteins (TOLLIPs), suppressor of cytokine signalling (SOCS) proteins and myeloid cell-associated immunoglobulin-like receptors (MAIRs; also known as CD300 and TAM receptors). Some of these negative signalling systems affect innate immune responses to virus infections. For example, A20 terminates nuclear factor-κB signalling and IRAKM inhibits TLR and IL-1β-induced signalling[58]. SOCS proteins inhibit cytokine signalling and are induced as a result of IL-10 receptor and TAM receptor signalling in macrophages and granulocytes. However some viruses use such pathways for their entry and enhanced tissue tropism. For example, filoviruses (such as Ebola virus and Marburg virus) exploit TAM receptors. After infection with filoviruses, innate cells secrete high levels of pro-inflammatory cytokines, such as type I IFNs. However, SOCS proteins are also induced as a result of TAM signalling[140]. Therefore, it is possible that although the use of these receptors by some viruses promotes infection and causes damage to the host, the subsequent signalling events induced might also moderate immune-mediated tissue damage. This scenario, however, needs to be formally investigated in the pathogenesis of viral infections.

Innate receptors
The receptors that are present either on the surface or in the cytoplasm of innate immune cells that recognize microbial surface patterns or their replicative products and induce cytokine production.

cytotoxic effects of viral components. Doses between these extremes can have a variable outcome from undetectable infection to tissue-damaging lesions. This issue has received surprisingly little formal study with virus infections, but it is a common practice for those who study viral pathogenesis to choose optimal doses of infection to evaluate their concepts. The dose and route of infection is expected to influence how successful the virus will be in gaining access to susceptible target cells and being transported by different types of DC to lymphoid tissues. Thus, it is clear from studies with protein antigens that the magnitude and quality of immune responses induced is influenced by the type of DCs that engage antigen[87]. With replicating agents such as viruses, dose effects might depend on the type of virus, the rates of replication and the virus-intrinsic properties such as expression of ligands for host innate immune receptors. For example, the dose of lentiviruses seems to have little effect, perhaps because potent infection is usually established by a single (founder) virion from the large numbers of virions (up to 10^6) that are transmitted to the host[88]. Experimental studies of simian immunodeficiency virus (SIV) infection of macaques also show little or no effect of dose on the outcome of infection[89]. By contrast, for cytopathic viruses, the dose of infection can influence the response pattern[90]. It is curious that for influenza virus, the dose of infection of mice also affects the range of cells that become infected, as well as the balance of the immune response that results[91]. At high doses of virus, DCs and alveolar epithelial cells become infected. Moreover, the infected DCs deliver apoptotic signals to CD8+ T cells, which are normally necessary for resolving infection. At lower doses of virus, DC infection does not occur and the protective CD8+ T cell response is not compromised.

Recently, an interesting and unexpected effect of infection dose was observed in chimpanzees infected with HBV[92]. HBV is a non-cytopathic virus, and both control of the virus and the development of immunopathological hepatic lesions are mediated by CD8+ T cells. Over a wide dose range (10^4–10^8 virions), the outcome of infection was similar, being controlled successfully 6–8 weeks after infection with minimal hepatitis. However, after administering a large dose (>10^8) of virus, 100% of hepatocytes became infected, the virus reached high levels for at least 16 weeks and the animals developed chronic active hepatitis. Unexpectedly, animals infected with a very low dose (100 virons or less) had a comparable immunopathological outcome to those infected with a large dose. Reasons for this are still uncertain, but it is possible that at low doses the virus can go undetected by the immune system and fail to induce priming of CD4+ T cells, which are needed to provide help to mount a protective CD8+ T cell response. Furthermore, if animals were depleted of CD4+ T cells and given the medium dose of virus they developed chronic active hepatitis. How these observations relate to HBV infection of humans needs evaluation.

Dose of infection might explain the variable outcome observed following infection by insect-transmitted flaviviruses. The flavivirus West Nile virus is becoming a common infection in the Western hemisphere but most infected individuals do not suffer any clinical consequences. However some individuals develop a life-threatening meningoencephalitis. In such individuals, the virus crosses the blood–brain barrier and lesions develop as a consequence of a viral antigen-specific T cell-mediated immunopathological reaction to infected cells[93]. One hypothesis explaining the pathological outcome is that it occurs in circumstances in which the virus replicates rapidly and exceeds the host's ability to constrain it, despite the induction of a neutralizing antibody response and numbers of functional T cells that would otherwise be protective[93]. This scenario is more likely to occur in those exposed to many mosquito bites (providing a high-dose infection), especially if the infected person is young, aged or has some degree of immunodeficiency. Curiously, some flaviviruses, including West Nile virus, stimulate TLR3 (which recognizes double-stranded DNA) and induce TNF production, and this may increase the permeability of the blood–brain barrier and allow entry of the virus to the CNS[94].

The route of infection can also affect the extent of tissue damage that ensues. For example, with HSV infection of humans, oral or genital infection usually results in lesions that resolve without long-term damage. However, infection of the eye can result in chronic inflammatory lesions that cause blindness[95]. Similarly, mice infected with corona virus or Theiler's murine encephalomyelitis virus can develop immunopathological lesions in the CNS, but this response only occurs if the virus is given intracerebrally or intranasally and fails to occur after systemic infection[96,97]. The meningitis that adult mice develop after LCMV infection occurs only if the virus is administered directly into the cerebrospinal fluid and is not evident if administered by other routes[98].

Influence of heterologous immunity. Heterologous immunity is the term used to describe the observation that exposure to one pathogen will generate an immune response against numerous antigenic epitopes derived from that pathogen some of which might cross-react with epitopes derived from other pathogens. Following infection with the second pathogen, the cross-reactive memory cells expand more rapidly and may dominate the overall response. However, this cross-reactive response may be of low avidity and poorly protective but may still be able to mediate tissue damage. These circumstances could explain the occurrence of severe disease (dengue haemorrhagic fever (DHF)) in a small minority of the 50 million people who are infected with dengue virus. DHF is characterized by a high fever, vascular leakage, hypotension, circulatory shock and some bleeding manifestations. It usually occurs in individuals who are already immune to one dengue virus strain and become infected with a heterologous strain. An initial explanation for the DHF syndrome was that it occurred because cross-reactive, but non-neutralizing, antibodies opsonized the virus, facilitating uptake by macrophages[99]. This was proposed to result in immune activation, abundant production of cytokines and vascular leakage. Other investigators now suggest that T cells are the main orchestrators of the disease and that they cross-react with epitopes primed by exposure to a different viral strain[99]. The expanded T cell populations are not protective but they can mediate a severe inflammatory reaction that includes the production of vascular endothelial growth factor A (VEGFA), the main mediator of vascular leakage. DHF does not occur as often as might be expected on the basis of this mechanism, which suggests that additional factors are also involved. These include viral virulence, the ability to replicate efficiently and host genetic factors. Clinical and experimental evidence for the proposed pathogenesis of DHF is reviewed in REF. 100.

Another tissue-damaging human disease that could be explained by the existence of heterologous immunity is infectious mononucleosis. The disease is debilitating and can last for weeks but it only occurs in a minority of usually young adults who have experienced a primary infection with EBV. In patients that develop infectious mononucleosis, there is a 5–20 fold increase their circulating T cells, most of which are viral antigen-specific CD8+ T cells. The pathogenesis of infectious mononucleosis is poorly understood but one provocative hypothesis is that the disease is the consequence of heterologous immunity, with infectious mononucleosis only occurring in individuals with EBV-cross-reactive T cells at the time of infection[101]. Such cross-reactive T cells are proposed to expand more rapidly than EBV-specific naive T cells induced following infection. However, the cross-reactive cells that dominate the response have low affinity for the virus antigen-expressing cells and cannot adequately control the infection, thereby setting the stage for chronic immunopathology. Supporting this concept, cross-reactivity between the influenza virus matrix protein and the EBV BMLF1 protein has been noted[102]. Experimental evidence that heterologous immunity can account for immunopathological responses in some but not all

animals was provided by Kim and colleagues[103]. Other examples of cross-reactivity between different pathogens that influence disease patterns are reviewed in REF. 104.

Host genetics and the 'virome'. Variation in clinical responses of individuals to virus infections is influenced by the host genotype. Virulent infectious agents are assumed to have helped to shape our genome and are responsible for the extreme polymorphisms of many loci involved in MHC antigen processing and presentation[105]. There is evidence that the outcome of the virus infection is affected by the HLA alleles expressed[106], but the influence is usually modest. Thus, resistance to pathogens, including viruses, is directed by several genes that act at different stages of the virus–host interaction. For example, at least 250 genes are estimated to affect the outcome of infection by HIV[107]. As a result, the absence or malfunction of a single gene would probably have a negative or minimal effect on the outcome of a virus infection. Exceptions to this generalization include the primary immunodeficiencies that arise from rare monogenic defects and lead to increased susceptibility to various virus infections[108]. Mutations of genes encoding viral receptors and co-receptors can also influence disease susceptibility. For example, individuals with a homozygous 32 base pair deletion in CC-chemokine receptor 5 (*CCR5*, the entry co-receptor for X5 HIV) have greater resistance to HIV than heterozygous individuals[109]. Another example is that non-secretors of ABO blood groups are refractory to diarrhoea caused by Norwalk virus[110]. Mutations in genes that encode proteins involved in innate defence, such as the TLRs, can affect the clinical expression of some infections, but so far little has been reported for viruses. One example is a mutation in *UNC93B*, which encodes a transmembrane protein involved in TLR signalling[111]. Another is a loss of function mutation of TLR3 (REF. 74). Both defects result in defective cytokine production, especially IFNα and IFNβ, in response to infection with HSV-1. Affected children develop herpes simplex encephalitis[74,112] but, curiously, not other problems with HSV infection or other viruses.

A more common scenario that accounts for more severe disease following virus infection is polymorphisms in a few or many genes. Investigations on this topic have focused on HIV (reviewed in REFS 106,113) but most changes detected so far have been minor, probably because several genes affect resistance. Genetic factors have not yet been shown to explain the finding that ~1% of HIV-infected patients control their infection long term without treatment[114].

In addition to host genetics affecting the pattern of disease, other sources of genetic material in the host could influence the outcome of infection. These are the endogenous retrovirus elements, some of which are transcriptionally active, that are estimated to contribute to 8–9% of total human DNA[115]. The other sources are exogenous viruses that establish persistent infections and are mainly not retroviruses. According to a recent review, every individual may harbour several (8–12) different chronic asymptomatic viral infections that lie

Dengue haemorrhagic fever
A viral disease transmitted by the bites of *Aedes egypti* mosquitos that carry dengue virus and is characterized by headache, fever, rash and evidence of haemorrhage in the body.

Infectious mononucleosis
A viral disease caused by infection with Epstein–Barr virus most commonly during adolescence and young adulthood. The classical symptoms include fever, sore throat and swollen lymph glands, especially in the neck.

REVIEWS

Virome
The total virus-derived genetic material present in the host owing to integrated or persistent exogenous viruses.

undetected[59]. Together these endogenous and exogenous viruses have been referred to as the 'virome'[59]. Already it is known that endogenous retroviruses could help to shape the T cell repertoire, deleting some specificities and expanding others[116]. Resident exogenous viruses might also influence the T cell repertoire and the activity status of the innate immune system, causing, for example, the production of cytokines and altered antigen presentation efficiency of DCs, but this needs to be formally shown. These effects will influence the balance of the response by individuals to exogenous agents. With technological advances in detecting both host gene polymorphisms and the virome, we anticipate that the influence of these factors on the outcome of virus infection will soon be better understood. This knowledge might provide clues to customize successful preventative and therapeutic approaches for viral infection and associated immunopathology.

Conclusions

Whether a virus infection results in severe, sometimes prolonged, lesions or is resolved with minimal bystander tissue damage depends on numerous factors. Some viruses (for example, HIV and HCV) have intrinsic properties that make immune control difficult, and attempts by the host immune system to achieve control results in notable tissue damage. Other infectious agents (for example, many herpesviruses) are successfully controlled in most individuals, but tissue damage occurs in those individuals that have predisposing genetic or acquired problems affecting one or more components of innate or adaptive immune system. Finally, some infections that are normally well controlled can cause extensive tissue damage under unusual circumstances. These might relate to the dose or route of exposure, the age of infection, host genetics and priming with cross-reacting viruses or co-infection with other agents.

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DATABASES
UniProtKB: http://www.uniprot.org
FOXP3 | galectin 9 | IL-10 | LAG3 | PD1 | PDL1 | RIG-I | TIM3 | TLR3 | TLR7 | TLR8 | TLR9 | TNF | UNC93B | VEGFA

FURTHER INFORMATION
Barry T. Rouse's homepage:
http://www.vet.utk.edu/faculty/rouse.php

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