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REVIEW

Innate and adaptive immune responses against picornaviruses and their counteractions: An overview

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Abstract

Picornaviruses, small positive-stranded RNA viruses, cause a wide range of diseases which is based on their differential tissue and cell type tropisms. This diversity is reflected by the immune responses, both innate and adaptive, induced after infection, and the subsequent interactions of the viruses with the immune system. The defense mechanisms of the host and the countermeasures of the virus significantly contribute to the pathogenesis of the infections. Important human pathogens are poliovirus, coxsackievirus, human rhinovirus and hepatitis A virus. These viruses are the best-studied members of the family, and in this review we want to present the major aspects of the reciprocal effects between the immune system and these viruses.

Key words: Picornaviruses and infection; Poliovirus; Coxsackievirus; Human rhinovirus; Hepatitis A virus; Adaptive immune system; Innate immune system; Antibody response and inflammation; Apoptosis; Interferon and cytokines

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INTRODUCTION

The picornavirus family represents a diverse group of viruses that are classified within 12 genera[1] (Table 1). These viruses cause a variety of human and animal diseases, including the common cold [human rhinoviruses (HRV)], myocarditis [coxsackie viruses (CV)], hepatitis [hepatitis A virus (HAV)] and poliomyelitis [poliovirus (PV)]. Because of their clinical relevance, these human pathogens, which except the hepatovirus HAV are members of the enterovirus genus, are the best-studied members of the family[2-5]. Although many details about the replication of these viruses are known[6,7] the pathogenesis of the heterogeneous clinical appearances and manifestations of the particular diseases, varying between asymptomatic and fatal, is poorly understood, but is closely linked to the immune responses induced after infection. Therefore, knowledge of the specific immunological activities following the entry of these viruses into the human host will provide the basis for a better understanding of the pathogenic processes.

The spherical, nonenveloped virions of picornaviruses range in diameter between 27-30 nm. The genome is a positive-strand RNA of 7000 to 9000 nucleotides covalently linked at the 5' end to the viral protein 3B (VPg) and is translated cap-independently by internal ribosomal entry into a polyprotein (VP4-VP2-VP3-VP1-2A-2B-2C-3A-3B-3C-3D), which yields the eleven proteins through various independently functioning intermediates, upon cleavage by viral proteases. Replication occurs in the cytoplasm in association with intracellular membranes. Picornaviruses are usually considered to be

released from infected cells by cell lysis[8], which applies for the cytopathogenic rhino-, coxsackie- and PVs, but not for HAV[9], for which the release process is not known. However, damage to tissues results not only directly from virus replication, but also from the host response to infection.

The host immune response against picornaviruses is diverse and complex, and this is reflected by the numerous data obtained in studies particularly with PV, CV, RV and HAV, and this review discusses various aspects of the immunology of these viruses.

The host fights virus infections by employing various mechanisms, including cytokine release, antibody production and cytotoxic T cell (CTL) activation. The importance of each mechanism, however, strongly varies according to the virus concerned.

As a large part of the infections with any of these four viruses proceeds asymptomatically, it can be assumed that the innate immune system, which responds within minutes after viral entry into host cells[10], is able to block viral replication to a certain degree. Sensing of specific structures of the viral nucleic acid like double-stranded RNAs, which occur as replicative intermediates and are recognized as pathogen associated molecular patterns, is accomplished in the cytoplasm by Toll-like receptor (TLR)3, which is associated with intracellular vesicles, or by the sensors retinoic acid-inducible gene I (RIG-I) and melanoma differentiation-associated gene 5 (MDA-5)[11] resulting in synthesis of cytokines with strong antiviral activity, like type I interferon (IFN). MDA-5, not RIG-I, is believed to be crucial for sensing infection with picornaviruses. This was concluded from studies with mice lacking the mda-5 gene. These mice are deficient in the production of type I IFN in response to the cardiovirus enzephalomyocarditis virus (EMCV), and the animals showed a higher susceptibility to infection[12,13]. But sensing of picornaviral RNA seems to be more complex, and the other sensors might also be involved, as overproduction of RIG-I in cultured cells is also able to reduce EMCV replication[14]. On the other hand, PV, CV, HRV as well as HAV have developed mechanisms to interfere with the signaling from the above mentioned sensors, although in different ways. This ability of the viruses seems to be necessary firstly to establish infection and secondly, to maintain replication for a longer time, as activation of the virus specific adaptive immune response by a specific cytokine mix generated during the innate response is retarded.

After primary infection, antibodies seem in general to be important to control viral viremic spread within the infected tissue as well as to distant further organs, and thus to retard the severity of the disease. Infections with PV and CV seem to be controlled efficiently by antibodies, as prolonged replication of PV occurs in immunodeficient patients[15] and prolonged excretion of coxsackievirus as well as chronic encephalitis after coxsackievirus infection was observed in patients with agammaglobulinemia[16-20]. This is supported by the finding, using $CD4^+$ T-cell deficient mice, that both PV and CV efficiently induce B cells to proliferate and produce IgM independent from T-cell help (TI IgM)[21-24]. This TI antibody response results from extensive B-cell receptor cross linking by the highly organized, repetitive virion structure and is postulated to be a characteristic of antibody-controlled cytolytic viruses[24]. In contrast, HRV seems to be controlled by the innate immune response as the antibody response appears after recovery from illness[25] and HAV seems to be eliminated by CTL[26,27]. Upon infection, these four viruses are expected to induce the production of secretory IgA (SIgA), serum IgA (sIgA) and IgG, which is due to their route of transmission. PV, CV and HAV are transmitted fecal-orally, whereas HRV is transmitted by the respiratory route. But there are significant differences between the viruses in the time courses of the different antibody classes as well as of the antibody responses. For example, the IgG response after infection with HAV is strongly delayed[28,29] and only a weak antibody response against HRV, which is boosted after resolution of the symptoms, develops[25]. It seems at least to be the rule for all four viruses that antibodies are critical to prevent reinfections. Even during asymptomatic courses of the diseases, production of neutralizing antibodies may be induced (occult immunization). In order to counteract this effect, polio- and coxsackieviruses form serotypes (PV: 3 serotypes, CV: 29 serotypes) which are defined as different viral strains that do not elicit cross-neutralizing antibodies. This enables the viruses to evade antibody-controlled reinfections and to infect the same individual several times by a different serotype despite the presence of possibly high titers of neutralizing antibodies and cross-reactive T-cell help against the first serotype. This also seems to apply for rhinovirus, which forms 102 serotypes, despite its weak and apparently delayed antibody response. Only in the case of HAV, which exists as only one serotype, are reinfections efficiently prevented by anti-HAV IgG induced by the first infection.

In the following sections the specific interactions between the different viruses and the immune system will be described.

ADAPTIVE IMMUNE RESPONSE

In general and on average, the adaptive immune response during viral infections is induced 3 to 5 d after the infection occurred, a time point when infections are established and the amount of progeny virus reaches a level required to activate the adaptive response by assistance of cytokines, which are released during the innate immune response. Before the $CD8^+$ T-cell response (CTL) reaches its peak 7 to 10 d after the infection, natural killer cells (NK cells) are present. The T-cell response decreases within 3 to 4 wk, but memory and splenic $CD8^+$ T-cells remain present. Antibodies produced by the adaptive B-cell response are barely detectable in the acute, symptomatic stage of the disease, but increase over a period of 2 to 4 wk. Virus and virus infected cells are normally eliminated 2 wk after infection and serum antibody as well as memory B and T cells remain.

Table 1 Picornavirus family

Genus	Normal host organism	Including for example
Aphtovirus	Cattle, swine	Foot-and-mouth disease virus
Cardiovirus	Humans, small rodents	Encephalomyocarditis virus Saffold virus
Enterovirus	Humans, cattle, swine	Poliovirus Coxsackievirus Rhinovirus
Hepatovirus	Humans	Hepatitis A virus
Parechovirus	Humans, small rodents	Human Parechovirus Ljungan virus
Erbovirus	Horses	Equine rhinitis B virus
Kobuvirus	Cattle	Aichi virus
Teschovirus	Swine	Porcine teschovirus
Sapelovirus	Birds, swine	Avian sapelovirus Porcine sapelovirus
Senecavirus	Swine	Seneca valley virus
Tremovirus	Birds	Avian encephalomyelitis virus
Avihepatovirus	Birds	Duck hepatitis A virus

Some viruses infecting bats (Juruaca virus), fish (Bluegill virus), reptiles, amphibians and ticks (Sikhote Alyn virus, Syr-Dorya Valley fever virus) are not classified within a genus so far. Plant picornaviruses differ from the animal viruses in some properties and have been classified into the family Secoviruses.

Whereas the adaptive immune response to polio- and CV roughly follows the above-described general scheme, the adaptive immune responses to human rhinovirus and HAV significantly deviate from the average course. In general, the adaptive response is required for complete virus clearance, and there is considerable data about the antibody responses to these four viruses (Figure 1) but, with the exception of HAV, little is known about the CTL response, and the role of these T cells is controversially debated. The CTL response against HAV which is the only non-cytopathogenic virus presented here is well investigated and it is shown that the symptoms of hepatitis A can be attributed to an immunopathogenic process caused by the activity of HAV-specific CTLs.

Neutralization of picornaviruses is mediated through antigenic sites, which are conformational, discontinuous and complex structures formed on the surface of the virions by exposed loops between the β-strands of certain structural proteins (structural proteins of picornaviruses building the surface of the capsid are VP1, VP2 and VP3; VP4 lines the inside of the viral particle). PVs have three distinct antigenic sites[30,31], which have been exactly identified. One antigenic site is formed by amino acids of the structural protein VP1 (aa 90-100, 220-223 and 286-290), the second site includes residues from VP1 and VP2 (aa 164-172) and the third site includes residues from VP1 and VP3 (aa 58-60 and 70-80). Within coxsackievirus capsids conformational and linear antigenic sites were found, which include residues from VP1, VP2 and VP3[32-34]. HRV exhibit four different antigenic sites, which are also formed by residues from VP1, VP2 and VP3[35]. HAV holds only one immunodominant antigenic site, which contains amino acid residues contributed by VP1 and VP3[36,37]. Three complementary mechanisms of neutralization are assumed[38]. Firstly, antibodies bound to the virus particle interfere with the attachment to the cellular receptor. Secondly, neutralization is a result of antibody-mediated aggregation of virions, which prevents attachment and uptake of virus, and thirdly, binding of antibodies to separate structural subunits within the capsid structure inhibits uncoating.

In the following, an overview of the adaptive immune responses against PV, CV, HRV and HAV is given.

PV

After fecal-oral transmission, the major site of replication is the intestinal tract (epithelia and Peyer's patches). After a mean incubation time of 7 d, influenza-like symptoms develop, from which the patient recovers within a few days. Fecal excretion of PV occurs shortly after infection and persists for approximately 7 wk, and a short viremic phase appears between 3 to 7 d after infection. Besides this abortive poliomyelitis, nonparalytic poliomyelitis may occur in 1%-2% of the infections with viral invasion of the CNS leading to meningitis and muscle spasm. The illness lasts for approximately 6 d. In up to 2% of the cases paralytic poliomyelitis occurs, and in 80% of these patients residual paralysis persists.

Neutralizing anti-PV IgM antibodies appear 3 d after infection, reach their peak titer after 9 d and disappear in the course of 4 wk[39-41] (Figure 1).

The anti-PV IgG response is also briskly appearing 3-4 d after exposure. These antibodies reach the peak titer 3-4 wk after infection and persist for years, perhaps lifelong[39-44]. The antibodies seem to be responsible for controlling viremia, as the termination of viremia immediately follows the detection of neutralizing antibodies (Figure 1). Already low levels of circulating anti-PV antibody, including passively given immune globulin, are able to prevent the paralytic disease. This indicates that infection of the CNS requires or is at least supported by viral spread through blood, and therefore significantly depends on the velocity and strength of the antibody response[45]. However, virus excretion continues for about 1 mo. Although it is not clear why shedding is going on for so long, the termination of shedding and final viral clearance seem also to be mediated by antibodies because hypogammaglobulinemia may result in persistent excretion for years[46] and because T-cell deficiency does not result in persistent viral excretion[47,48].

Mucosal anti-PV IgA (SIgA) is detectable 1 wk after infection in pharyngeal and stool samples, whereas sIgA appears 3 wk post exposure (Figure 1). Both responses reach their maximum levels approximately 4 wk after infection, but SIgA with a higher magnitude than sIgA[39-41]. The source of these antibodies is not known. The mucosal immunity to PV provides substantial resistance against secondary infections[39], and seems to play an important role in preventing spread of PV. This is evident, as in contrast to inactivated PV vaccine, which is less effective than the live vaccine in stimulating enteric immunity, the

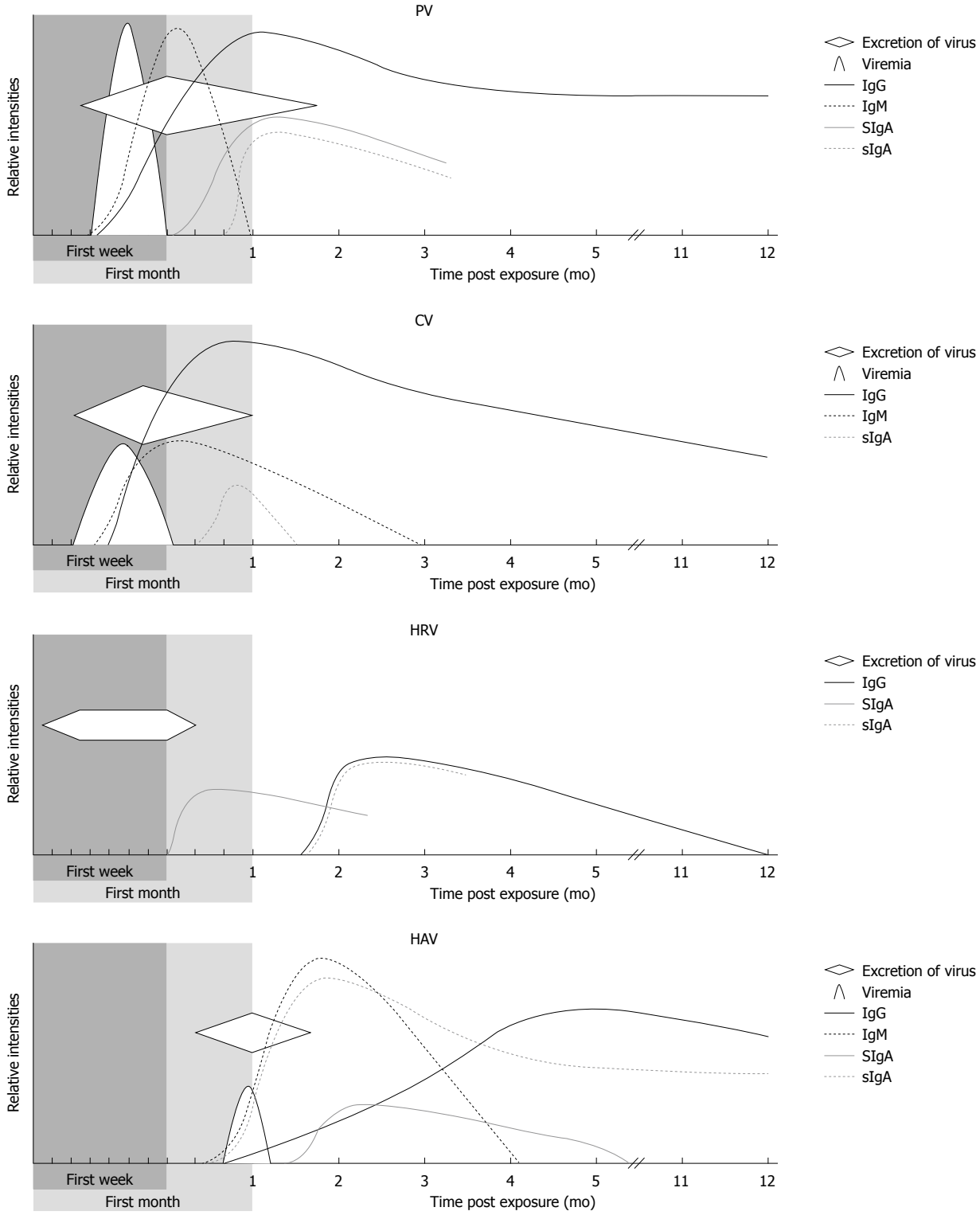

Figure 1 Time courses of viral excretion, viremia and of the antibody responses after infection with poliovirus, coxsackievirus, human rhinovirus and hepatitis A virus. This figure schematically shows the mean duration and relative intensity of viral spread and the antibody responses against the viruses. PV: Poliovirus; CV: Coxsackievirus; HRV: Human rhinovirus; HAV: Hepatitis A virus; SIgA: Secretory IgA; sIgA: Serum IgA.

oral live-attenuated PV vaccine is much more effective in preventing intestinal infection and has a much greater dampening effect on fecal shedding of PV[49,50]. Both vaccines, however, induce similar levels of circulating antibodies. As mentioned above, the mechanism by which anti-PV antibodies terminate viral shedding and are able to clear infection is not known. However, it can be assumed that in the intestinal epithelium the cell-to-cell spread of progeny viruses, which are released after lysis of the infected cells, is interrupted by the enteric anti-PV IgA antibodies[41]. Alternatively, antibody-mediated lysis of infected cells could also be involved.

In contrast to the neutralizing antibody response to PV, much less is known about the adaptive T-cell responses and their probable role in PV infections. PV-specific $CD4^+$ T cells are induced in vaccinated individuals, and epitopes have been identified[51,52]. The induction may occur by dendritic cells and macrophages infected with PV[53]. This also shows that HLA class Ⅱ presentation remains intact in infected antigen presenting cells. The resultant $CD4^+$ T cells were also able to produce IFN-γ and lyse infected target cells[53]. The cytolytic ability together with the ability to secrete IFN-γ allows the assumption that PV-specific $CD4^+$ T cells may play a role in virus clearance. Furthermore, stimulation of PV-specific cytotoxic $CD8^+$ T-cell (CTL) responses by infected macrophages could be demonstrated, and these CTLs secreted IFN-γ[53]. This implies that virus clearance is not only due to the $CD4^+$ T-cell/antibody response, but that the CTL response might also play a role. Since the 1950s, inactivated and live-attenuated PV vaccines have been available[50].

Coxsackie virus

After respiratory and fecal-oral transmission, respectively, the incubation time is approximately 5 d, but may last for up to 35 d. These viruses cause a systemic disease, both acute and chronic, with a wide variety of symptoms. Besides infection of the epithelial tissues, the viruses exhibit myotropism and a tendency to infect the central and peripheral nervous system by humoral spread, and the acute clinical appearances may range from influenza-like symptoms (minor summer illness) to myocarditis, aseptic meningitis as well as myelitis. The duration of acute illness is usually between 3 and 8 d. Post-acute symptoms include myocarditis and pericarditis, which may persist for weeks[54-58] and infections have been linked to the induction of autoimmune diseases such as chronic myocarditis and type 1 diabetes. Excretion in feces and nasal secretions, respectively, occurs between days 2 and 28 after infection, reaching its peak 6 d post exposure. A viremic phase may be observed from days 2 till 8 after infection.

Most of the data available on the courses of the antibody responses were obtained by experimental respiratory infections in volunteers or with the mouse model. CV-neutralizing IgM antibodies, which may be serotype-specific or cross-reactive, appear 3 d after exposure (Figure 1). They reach their maximum titer level 1 wk after infection and typically disappear in the course of 3 mo[55-57,59,60].

Little is known on the anti-CV IgA responses. However, the sIgA and IgM responses seem to interfere with each other[60], which means the higher the one is the lower the other is with regard to their relative values. In some patients an IgA response is not detectable at all throughout the course of the infection. The presence of anti-CV IgA antibodies is detectable approximately 15 d post infection for the first time (Figure 1). These antibodies reach their peak level 21 d after exposure and disappear in the course of 6 wk[60].

The anti-CV IgG response approximately appears 4 d after exposure (Figure 1). These antibodies reach their maximum titer 2-3 wk after infection and may persist for years[55-57,61]. The humoral response plays a prominent role in limiting virus spread to different tissues by blood as well as in viral clearance[62]. In patients with agammaglobulinemia the infection spread to, and persisted in, the central nervous system[17,19,63]. CV infection of B cell-deficient mice results in chronic, high-titer infections in multiple organs, like heart, liver, lung and pancreas, and transfer of immune B cells at least transiently resulted in clearance of CV from all tissues[64]. Furthermore, the importance of antibodies is demonstrated by the finding that passive transfer of immune serum globulin reduces viral titers and symptoms in patients[65]. As demonstrated by passive immunizations with sera from fully recovered patients (within 72 h after infection), the presence of antibodies is also sufficient to prevent secondary infections.

In contrast to the evidently central protective role of anti-CV antibodies during coxsackievirus infections, some studies have shown that anti-CV IgG-mediated CV infection of monocytic/macrophagic cell lines, lymphocytes and plasmacytoid dendritic cells (pDC) *via* Fc receptors is possible[64,66-68], thus showing that IgG antibodies might contribute to virus dissemination in the body, enhance infection and exacerbate disease under certain circumstances. This effect must be taken into consideration in the development of vaccines.

The role of the T-cell responses in coxsackievirus infections is not clear. The data obtained with different mouse strains or different virus variants are controversial[21,62,69-74]. Using T cells directed against lymphocytic choriomeningitis virus-specific epitopes as sensors to evaluate antigen presentation by a recombinant CV expressing these epitopes, it was shown that the virus strongly inhibits antigen presentation through the MHC class I pathway[75], and therefore is able to evade $CD8^+$ T-cell immunity. In contrast to the low presentation by MHC class I molecules, MHC class Ⅱ-restricted presentation occurred at least at a level that might enable a primary CV-specific $CD4^+$ T-cell response[75].

Coxsackievirus infections are suspected to be involved in the induction of autoimmune reactions particularly against cardiac cells and pancreatic islet cells. However, a discussion of this aspect is beyond the scope of this review. In short, these reactions are directed against self-antigens by pre-existing auto-reactive lymphocytes. Coxsackieviruses might contribute to the activation of these lymphocytes by making more antigens available by the release of cellular components, which in addition might present novel, cryptic epitopes resulting from the cleavage of cellular proteins by the viral proteases 2A and 3C, during cytopathogenic infection and by promoting responses to these new antigens by presentation in an inflammatory context, which stimulates migration of lymphocytes to the relevant tissues[73]. There is no vaccine for active immunization against CV infections.

Human rhinovirus

After transmission by the respiratory route (sneezes) or

after infection by self-inoculation (hand into nose contact), the mean incubation time is 2 d. The typical symptoms are these of the common cold (rhinorrhea: running nose, swelling of the epithelial tissue), which last on average for 3 d. Virus shedding in the nasal secretions already occurs 8-10 h after exposure, reaches maximum levels between days 2-7 and sometimes may continue till day 14 after infection at very low levels[25,57,76]. Besides this common course of infection, virus might spread from the ciliated epithelial cells of the upper respiratory tract into the lower airways resulting in asthmatic exacerbations[77].

Anti-HRV SIgA in nasal secretions occur approximately 7 d after infection, a time point when the illness had subsided already, reaching their maximum level approximately 16 d post exposure[25] (Figure 1). In contrast to SIgA, sIgA to HRV does not increase before 6 wk after infection (Figure 1). The same applies for the anti-HRV IgG response, which develops between 6 and 7 wk after exposure and persists for approximately 1 year[25] (Figure 1). However, during secondary infections detectable amounts of serum antibodies to HRV may develop between 1 and 2 wk after infection, reaching their peak titer 5 wk post exposure[76,78].

The antibody response to HRV does not seem to play a role in virus spread and clearance, because it appears only after the end of the illness, and in persons with IgA deficiency and hypogammaglobulinemia normal recovery from illness occurs[79]. Furthermore, antibody production occurs on an average only in 50% of the cases and neutralizing antibodies, which do not show cross-reactivity, generally are produced in low amounts[76,78]. Therefore, protection by antibodies against secondary infections with HRV, which additionally appear in extraordinary different versions of serotypes, is strongly limited.

The T-cell response to HRV is incompletely understood. An increase in lymphocytes 3-4 d after exposure can be observed in nasal secretions. Specific $CD4^+$ T-cell clones, which secreted the Th-1 type cytokine IFN-γ, could be isolated in peripheral blood from persons with previous disease[80,81]. These T cells showed serotype cross-reactivity[80]. This implies that $CD4^+$ T cells can be activated by shared viral determinants, and can induce recall T-cell responses to HRV. One study suggests that eosinophils might act as antigen-presenting cells, which activate $CD4^+$ T cells[82]. No data are available on an involvement of cytotoxic $CD8^+$ T cells (CTL). There is no vaccine (neither passive nor active) against HRV infections.

HAV

After oral uptake, the mean incubation period is 4 wk. The preicteric period of normally 5 d with unspecific symptoms (nausea, malaise, headache) ceases with the onset of jaundice, which lasts on average for 3 wk. Fecal shedding of HAV already occurs during the late incubation period when no clinical symptoms are observable, and lasts for approximately 3 wk. The fecal excretion reaches its maximum just before the onset of hepatocellular injury and terminates about the time when the IgG antibody response is detectable (Figure 1). Viremia occurs a few days before and during the early acute stage and roughly parallels the fecal shedding, but at a lower magnitude. Besides this common course of infection, prolonged and relapsing courses occur in up to 25% of the patients[83].

Anti-HAV IgM antibodies are present in almost all patients at the onset of the symptoms (3-4 wk post infection). These antibodies reach their maximum level 2 mo post exposure, have only weak neutralizing activity and typically disappear in the course of 3 mo (Figure 1). But in the course of prolonged courses, IgM can be detected up to 1 year after onset of icterus[28,29,84,85].

Anti-HAV IgA antibodies are also detectable at the onset of the symptoms in blood (sIgA) (Figure 1). This response reaches its peak titer 50 d post exposure and may last for more than 5 years[28,29,85,86]. The majority of the IgA remains in circulation as sIgA and is not secreted into the intestinal tract as SIgA by the polymeric immunoglobulin receptor (pIgR) pathway. But a significant fraction of the sIgA may be released into the intestines *via* bile by liver functions mediated by the hepatocellular IgA-specific asialoglycoprotein receptor (ASGPR), and fecal samples contain IgA from 5 to 6 wk till 3 to 6 mo post infection[87-91] (Figure 1). Salivary anti-HAV IgA is also detectable in patients, which course parallels that of fecal IgA[90]. But the role of SIgA in the protection against HAV infections appears to be limited, as neutralizing activity in most human specimens is barely detectable, which correlates with animal studies[90]. Results obtained with cultured cells as well as in a mouse model suggest that HAV-specific IgA can serve as a carrier molecule for a liver-directed transport of HAV, supporting and enhancing the hepatotropic infection by uptake of HAV/IgA immunocomplexes *via* the ASGPR[91,92]. It could be shown that IgA-coated HAV is translocalized antivectorially from the apical to the basolateral site of cultured polarized epithelial cells *via* the pIgR[93], and it was assumed that fecal HAV/IgA[87,94], whose stability enables its fecal-oral transmission[91], is able to support the primary infection utilizing the IgA receptors. Furthermore, it was postulated that an enterohepatic cycling of HAV may be established during infection by HAV/IgA resulting in endogenous reinfections of the liver until large amounts of highly avid IgG displace the IgA in the HAV/IgA complexes[92]. Depending on the individual immune response, this mechanism may play a role in the development of the different courses of hepatitis A[92]. With respect to the anti-HAV IgA response in general, it is not clear by which processes and mechanisms induction occurs.

Neutralizing anti-HAV IgG antibodies are detectable 3-4 wk post infection for the first time, but this response develops slowly, reaching its peak titer 4 to 5 mo post infection (Figure 1), a time point late in the convalescence phase[28,29,85]. Anti-HAV IgG persists lifelong, although the titer may fall to undetectable levels after several decades. Although the minimum level of neutralizing antibodies that protects against infection and disease is unknown, an estimate of a minimal protective level is approximately

20 mIU/mL blood. Circulating anti-HAV IgG of the developing IgG response may limit viremia and thus re-infections at different hepatic sites by progeny virus, but is sufficient to prevent subsequent secondary infections. Passive immunization with pooled immune serum globulin[95,96] of at least 100 IU anti-HAV can prevent the disease for up to 5 mo with a certainty of 80%-90%. Definite duration of protection by immune serum globulin is dose related[97-100]. Studies suggest that passive immunization does not always prevent infection, but ensures an asymptomatic course of the disease[101,102]. IgG is still used for post exposure prophylaxis. If administered within 2 wk after exposure, either development of the disease is prevented or the severity of the disease is attenuated as well as virus shedding is reduced[95,96,103]. Since 1992, inactivated vaccines are available[104-106], which protect against both infection and disease caused by all strains of HAV with 100% efficacy for at last 10 years. Live, attenuated vaccines have been developed using virus adapted to growth in cell culture[107], but were poorly immunogenic[108]. Nonetheless, such a vaccine has been widely used in China and appears to be capable of inducing protective levels of antibody[109]. However, as anti-HAV IgA might be induced by live vaccines and act as pathogenicity factor for hepatitis A (see above), this approach might not be advantageous as compared to the inactivated vaccines.

Clearly, the antibody response to HAV prevents secondary infections and may limit viral spread during infection. But with regard to viral clearance and destruction of infected hepatocytes, anti-HAV antibodies do not seem to play a role. Destruction of infected hepatocytes by HAV-specific antibodies with or without the help of complement could not be demonstrated[29]. However, it has been shown that HAV-specific, HLA-restricted cytotoxic $CD8^+$ T lymphocytes (CTL) play a prominent role both in eliminating the virus and in causing liver injury (immunopathogenesis). CTLs were identified in liver biopsy specimens obtained during the acute infection[26,27]. Nearly 50% of the liver-infiltrating, cytotoxic T-cell clones displayed HAV-specific cytotoxicity. During activity the CTLs produced IFN-γ[27,110], which may stimulate HLA class I expression on hepatocytes and in the following promote upregulation of the normally low level display of antigen on liver cells resulting in more efficient destruction of infected cells by these CTLs. During this acute phase of infection only 1%-2% of the CTLs in peripheral blood showed HAV-specific cytotoxic activity[26], whereas 2-3 wk after onset of icterus[111], which means during the early convalescent phase, HAV-specific CTL activity reached peak levels in peripheral blood. This indicates that HAV-specific CTLs accumulate in the liver during the acute phase, and after the destruction of the infected hepatocytes leave the liver back into blood. Multiple dominant T-cell epitopes could be identified in the proteins VP1, VP2, VP3, 2B, 2C and mainly 3D[112]. This multitude of T-cell epitopes combined with an inhibitory effect of HAV on CTL-suppressing regulatory T cells during the acute phase of the disease[113] seems to result in a strong activity of HAV-specific CTLs leading to an efficient elimination of HAV, which might prevent persistence of the virus. Also NK T cells seem to be involved in the elimination of HAV and the destruction of hepatocytes[114].

INNATE IMMUNE RESPONSE

The innate immune system is designed to enable fast cell reactions to invading microorganisms. It is not aimed to respond to a specific pathogen, but pathogens are recognized by particular molecular patterns, which are specific for certain groups of pathogens (PAMP; pathogen-associated molecular pattern), but not found within cellular molecules. After recognition of viral molecular patterns, the synthesis of proteins, including a variety of cytokines and enzymes, and/or reactions, like apoptosis, are induced, which are able to interfere with the growth of the virus at the site of infection. Virus-specific molecular patterns are especially single-stranded RNA (ssRNA) and double-stranded RNA (dsRNA) (in the case of DNA viruses, unmethylated CpG DNA is additionally recognized by the TLR9). ssRNA represents viral RNA genomes either introduced by the invading virus or produced by virus replication, and dsRNA represents viral replication intermediates (in the case of dsRNA viruses it also represents the genome). As these viral nucleic acids can only be detected if they are freely present in the cytoplasm, sensing of viruses and induction of the cellular antiviral activities are only possible after the infection of cells has already occured. By far the most prominent reaction against viruses is the production and secretion of type I IFN by infected cells, resulting in the establishment of an antiviral state in the surrounding cells by expression of proteins with antiviral activity. Thus, viral spread in the infected tissue is contained. Type I IFN, which can be induced in virtually all cell types, represents numerous subtypes of IFN-α and a single IFN-β. The major cytoplasmatic recognition receptors are RIG-I[13,115,116] and MDA-5[12,13], which both are cytosolic and may associate with stress granules, as well as TLR3[117,118], which is localized in endosomal membranes. These three receptors activate the IKKε/TBK1 kinases [inhibitor of nuclear factor (NF)-κB kinase ε/TANK-binding kinase 1][119-122] *via* the adaptor proteins MAVS (mitochondrial antiviral signaling protein; RIG-I and MDA-5)[123-126] and TRIF (TIR domain-containing adaptor inducing IFN-β; TLR3)[127-129], respectively. These kinases phosphorylate interferon regulatory factor 3 (IRF-3), which results in IRF-3 dimerization and cytoplasmic-to-nuclear translocation[130,131], where it induces IFN-β transcription as a central component of the transcription complex[132,133]. Three additional transcription factors participating in the induction of IFN-β transcription are NF-κB, ATF-2 and c-Jun, which are activated by signaling pathways also starting from MAVS. After secretion, IFN-β binds to the type I IFN receptor (IFNAR1/2) on neighbouring cells, resulting in expression of a variety of interferon stimulated genes (ISGs) *via* the Jak/STAT signaling pathway, which additionally includes the transcription factor IRF-9 and the interferon

stimulated response element promoter element. In general, upon activation by viral stimuli these antiviral ISG proteins [e.g., protein kinase R (PKR) or oligoadenylate synthetase] affect the cellular, macromolecular synthesis (transcription, translation) and consequently viral growth. Induction of IFN-α requires the IFN-β-induced IRF-7, which is also activated by the IKKε/TBK1 kinases, but is not constitutively expressed as compared with IRF-3. Thereby, the effects of IFN-β are amplified in the course of the IFN response.

Besides induction of IFN synthesis in infected cells, apoptosis may be initiated by activation of caspases.

These antiviral effects are supported by cytokines, which are produced by monocytes/macrophages, dendritic cells, granulocytes (eosinophiles, basophiles and neutrophiles) and NK cells activated by cellular contents and debris released by the destruction of infected cells. For instance, cellular destruction may be caused by the cytolytic activity of cytopathogenic viruses. In this way, a hostile, inflammatory environment is created, which can be characterized by the presence and the amount of the different cytokines and of the different inflammatory mediators, which are induced by the cytokines in the cells at the site of infection (certain enzymes, prostaglandines/leukotriens, reactive oxygen intermediates). Simultaneously, the adaptive immune response is activated by effects of the cytokines (e.g., upregulation of antigen presentation).

In general, the effects caused by the innate immune system depend on the specific composition of the cytokine pattern, which is created by cell type-specific reactions of the cells involved in the antiviral response, including the leukocytes and the specialized cells of the tissue infected. Therefore, the innate immune response will vary according to the cell type infected. In addition, the response is influenced and modified in a specific manner by the ability of the viruses to interfere at certain sites of the cellular reactions (Figure 2). These specific interactions between host cell and virus significantly contribute to the pathogenesis of the infection, which can for example be clinically observed in the viral-specific course of the fever curve.

In the following, an overview of the interactions between PV, CV, HRV and HAV and the innate immune system is given.

PV

PV is partially resistant to type I IFN. In experiments using cells pre-treated with IFN-α, PV resistance against type I IFN correlated with the amount of virus infecting each cell[134], and it was shown that the viral protease 2A can inhibit the activity of ISG proteins. However, this ability depends on the cell type infected. In PV receptor-transgenic mice (only infectable because of this genetic modification), virus replication is limited to the central nervous system, whereas in mice which additionally lack the receptor for type I IFN, replication also occurs in liver, spleen and pancreas[135]. This presumably reflects cell type-specific antiviral effects of IFN which can not be inhibited by 2A. It is unknown which ISG proteins inhibit PV replication and by which mechanism 2A interferes with these proteins, but it was demonstrated that the IFN-inducible PKR is degraded by the PV protease 2A in cells infected with PV[136,137].

The release of IFN-β from cells infected with PV is repressed by a variety of mechanisms. Transcription, translation and secretion of IFN are affected by participation of the polioviral proteases 2A and 3C as well as by the protein 3A, which is able to interact with intracellular membranes. MDA-5 is degraded during infection in a proteasome- and caspase-dependent manner[138]. Although the mechanism involved is not fully understood, MDA-5 cleavage might be triggered by the proteases 2A and 3C, respectively (Figure 2). Both 2A and 3C mediate PV-induced apoptosis[139,140], causing mitochondrial damage, release of cytochrome c, and activation of the caspases 3 and 9[141]. The caspases might produce cleavage products of MDA-5, which are substrates for the proteasome. The apparent disadvantage of inducing apoptosis in cells infected can be compensated by the fast replication of PV, and the apoptosis-induced MDA-5 cleavage resulting in suppression of IFN synthesis provides the opportunity that newly synthesized viruses are able to infect neighbouring cells, in which no antiviral status is established. However, inhibition of MDA-5 cleavage did not influence PV replication[138], indicating that alternative signaling pathways for IFN induction are available after PV infection. In this context it is remarkable that PV-3C cleaves RIG-I[142]. This might indicate that this sensor of viral nucleic acids, too, is involved in the recognition of picornaviral RNA, although it is believed that MDA-5 is the major sensor receptor. Not only are both cytoplasmatic RNA sensors cleaved during PV infections, but also is the mitochondrial protein MAVS that is transmitting the signal from the sensors downstream cleaved by the proteases 2A and 3C, in which 3C seems to be positioned at the mitochondrial membrane by 3A of the processing intermediate 3ABC[143]. Therefore, different sites inside the RIG-I/MDA-5 pathway are attacked by PV, which might result in cooperative or synergistic effects, and might compensate for the only partial resistance of PV to IFN.

The viral proteases are not only involved in the inactivation of components of the signaling pathway resulting in induction of IFN transcription, but also cleave other cellular proteins, including eIF4G[144] (cleaved by 2A), which is necessary for cap-dependent initiation of cellular protein translation, and PABP[145] (cleaved by 3C), resulting in an attenuation of IFN-β translation (Figure 2).

Besides inactivation of cellular proteins necessary for expression of IFN-β by proteolytic cleavage through viral proteases, a significant reduction in secretion of IFN-β as well as of the pro-inflammatory cytokine interleukin-6 (IL-6), is caused by localization of the viral 3A protein to the ER leading to an attenuation of the ER-to-Golgi traffic[146] (Figure 2). This mechanism results in a diminished IFN response as well as in an attenuation of

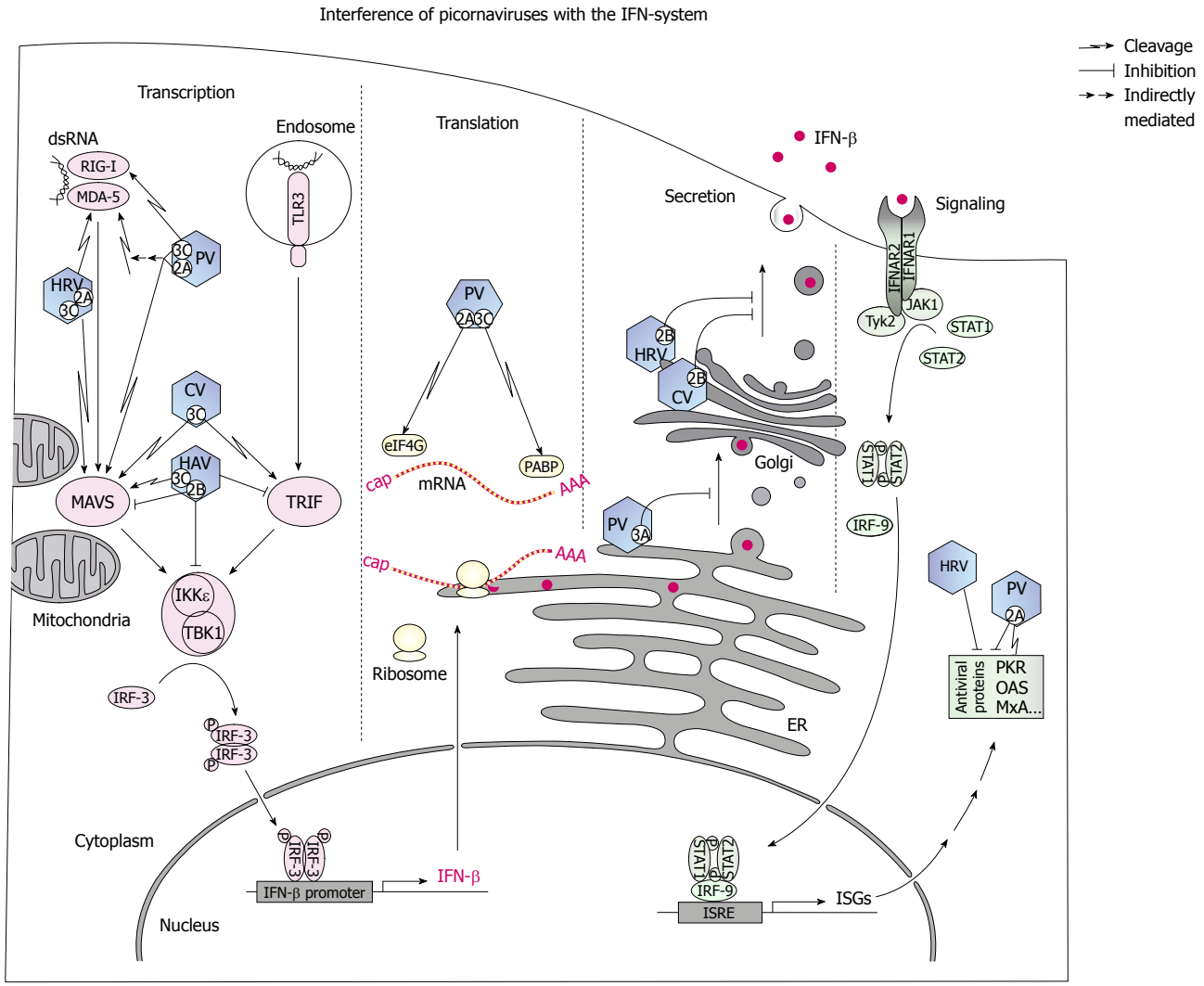

Figure 2 Interference of picornaviruses with the interferon system. This figure schematically shows the sites and effects of the interference of poliovirus, coxsackievirus, human rhinovirus and hepatitis A virus with the interferon-β response. For more details we refer to the text. PV: Poliovirus; CV: Coxsackievirus; HRV: Human rhinovirus; HAV: Hepatitis A virus; IFN: Interferon; IRF: Interferon regulatory factor; ISGs: Interferon stimulated genes; MDA: Melanoma differentiation-associated gene; dsRNA: Double-stranded RNA; PKR: Protein kinase R; TLR: Toll-like receptor; MAVS: Mitochondrial antiviral signaling protein; ISRE: Interferon stimulated response element; OAS: Oligoadenylate synthetase; RIG-I: Retinoic acid-inducible gene I.

inflammation. Additionally, the rate of MHC-I transport to the cell surface is reduced, resulting in an inhibition of antigen presentation and therefore of the adaptive $CD8^+$ T-cell response.

In summary, PV seems only to be able to interfere partially with certain sites of the signaling and synthetic pathways participating in the innate immune response to the virus. But the virus seems to be capable to dampen the innate responses to a certain degree by interference with multiple sites in these pathways, allowing the virus to establish infection.

Coxsackie virus

The innate immune response against CV was investigated in the presence of different post-acute symptoms, utilizing different cell types in cell culture experiments as well as different mouse strains and different virus strains, and accordingly, the available data is versatile. We will give a summary on the processes found that apply in general. CV is sensitive to IFN-β, and treatment of patients with myocardial virus persistence with this cytokine results in elimination of the virus[147]. The protective role of the IFN-β system was demonstrated in mice lacking the type I IFN receptor and in IFN-$\beta^{-/-}$ mice, respectively[148,149]. In these mice the susceptibility to infection as well as the severity of the disease was significantly increased. These findings correlate with results obtained with mice deficient in the genes for MDA-5[150,151] and TLR3[152], respectively. The pronounced effect on mortality in MDA-5/TLR3 double-knockout mice after CV infection might indicate a cooperative role of these receptors[151]. These results show that MDA-5 and TLR3 are involved in IFN-β induction during CV infections. However, this does not influence virus titers[151]. It is possible that type I IFN reduces mortality during infection independent of its effect on viral replication. Nevertheless, CV is able to attenuate the IFN response by protease 3C-mediated cleavage of the adaptor protein MAVS, which

transmits the signal from MDA-5 to the IRF-3 kinases, and the adaptor protein TRIF, which transmits the signal from TLR3 to the IRF-3 kinases[153] (Figure 2). Cleavage of these adaptors also inhibits apoptotic signaling. In addition, secretion of IFN and other cytokines, which are induced by other pathways, as well as MHC-I transport to the cell surface for antigen presentation, are inhibited by the viral protein 2B, which localizes to the Golgi complex, thus inhibiting trafficking through the Golgi[154-157] (Figure 2). The intercalation of CV-2B into the Golgi membranes also results in down-regulation of Ca^{2+} signaling between Golgi and mitochondria and consequently in suppression of the apoptotic cell response[158].

Besides TLR3, coxsackievirus infections can be also sensed by further TLRs[62], including TLR7 and TLR8[67,159], which recognize viral ssRNA. These receptors can mediate production of pro-inflammatory cytokines and type I IFNs in human cardiac cells and pDC. But this response seems to occur late in the course of the infection, after the antibody response to CV has developed, as TLR7 activation seems to appear after the IgG-mediated entry of CV into pDCs *via* the Fc receptor, and absence of MyD88, the adaptor molecule for TLR7, does not affect the mortality rate of CV infections[151]. Amazingly, TLR4, which is normally activated by bacterial lipopolysaccharides, appears to be activated by CV resulting in secretion of pro-inflammatory cytokines, which correlates with a more severe course of the disease[160-163]. However, the mechanism of activation by CV is unknown. Although CV can be recognized by several receptors sensing viral nucleic acids, TLR3 seems to play a critical, non-redundant role. TLR3 deficient mice are unable to control CV replication, and activation of alternative pathways is not sufficient to protect the host[152,164].

It has been demonstrated that several innate effector cell types, including NK cells, macrophages and dendritic cells are involved in the secretion of the cytokines and pro-inflammatory mediators during the innate response to CV[73]. Depletion of NK cells, which are involved in the maturation of DCs and activation of T cells, substantially increased CV titers in the heart or pancreas[165]. Concerning the role of macrophages, it has been demonstrated that inducible nitric oxid synthase expressing macrophages migrate to CV-infected tissues, that inhibition of this enzyme results in higher viral titers[166], and that adoptive transfer of macrophages from wild type mice has protective effects in TLR3-deficient mice by reducing cardiac disease and mortality following CV infection[152]. With regard to dendritic cells, their subset composition and functionality have an impact on the development of myocarditis[167].

The role of CV binding to the complement component C3 and activation of the alternative pathway[168] is not clear, but might be involved in the development of myocarditis by the effects of C3a and C5a on activation of leukocytes.

A whole series of different substances (cytokines, chemokines and mediators of inflammatory reactions) and cell types of the innate immune system show correlations with autoreactive processes following CV infection. However, it has not clearly been shown in which way they contribute to the disease. But the balance of timing, duration and amount of expression of the different cytokines, which depends on the strength of signaling from the different pathways and results in a certain cytokine pattern, seems to be important and critical for the development of an appropriate antiviral response that does not degenerate into autoimmunity (for review see Richer 2009[152]).

Human rhinovirus

During HRV infection, a variety of antiviral factors are released by the epithelial cells including the vasoactive peptide bradykinin and the pro-inflammatory cytokines IL-1β, tumor necrosis factor α, IL-6 and IL-8, which activate granulocytes, dendritic cells and monocytes to migrate to the site of infection[169,170]. IL-8 especially attracts neutrophiles, which might contribute to the exacerbation of asthma observed in infections[171]. Type I IFN, to which HRV is sensitive[172], is detectable in nasal secretions in approximately 30% of the patients[78], but up-regulation of the IFN-induced MxA protein in the nasal mucosa could not be detected[173]. As HRV can replicate in certain cells pre-treated with IFN-α[134], the virus has the ability to interfere with the activity of ISG proteins and attenuate the effects of type I IFN. However, the mechanisms involved are unknown.

Although HRV seems to be eliminated by the innate immune responses, the virus has the ability to affect several components of the IFN-β induction pathway (Figure 2). At least certain types of HRV are able to cleave the cytosolic viral pattern recognition receptors MDA-5 (type 1a)[138] and RIG-I (type 16)[142], respectively. Cleavage of the mitochondrial protein MAVS also could be demonstrated during HRV 1a infection[143] (Figure 2). This cleavage is mediated by the viral proteases 2A and 3C. Here, the activity of 3C seems only to be displayed by the processing intermediate 3ABC, which is directed to the mitochondrial membrane by the function of 3A. However, 2A as well as 3C mediate the HRV-induced apoptosis[174], which has antiviral effects. But caspase-3, which is activated during apoptosis, is able to support the 2A/3C-mediated inhibition of MAVS signaling by cleavage of MAVS[143]. Furthermore, the secretion of cytokines, including IFN, is inhibited by HRV-2B, which localizes to the Golgi membranes resulting in the inhibition of the secretory pathway[157]. This effect might also delay MHC-I presentation. By this attenuation of the IFN-β response, the fast replicating HRV might gain time to establish infection at least locally and thus to secure its transmission.

HRV is also able to attenuate the inflammatory effects caused by the cytokines released from epithelial cells during infection by induction of IL-10 secretion in monocytes and macrophages[76,175]. The mechanism by which HRV causes this effect is unknown. IL-10 does not only inhibit the production of pro-inflammatory cytokines[176],

but also downregulates MHC class Ⅱ molecule expression[177], which results in inhibition of T cell activation. This inhibitory effect on T-cell stimulation might contribute to the delayed adaptive immune response against HRV and might be supported by additional viral effects on antigen presenting cells[76]. Although HRV does not infect leukocytes, the virus binds to these cells *via* the intercellular adhesion molecule-1[178], which serves as cellular receptor of the major group of HRV, and is important in leukocyte migration and stimulation of T-cell responses. This binding results in an enhanced adhesiveness of monocytes/macrophages[179], which thereby might be retained longer at the infected sites. As a result, delayed emigration of these cells to lymph nodes might occur, which in combination with an attenuated stimulatory effect on T-cell proliferation might inhibit T-cell activation. An additional inhibitory effect on the adaptive T-cell response might be due to HRV-induced upregulation of CD274 and sialoadhesin (Siglec-1) on dendritic cells[180]. Both molecules inhibit the T-cell stimulatory function of DCs, but the mechanisms involved are unknown.

HAV

Experimental elimination of HAV infections in human fibroblast cultures by exogenously added IFN-α/β showed that HAV is not resistant to these IFNs[9,181] but reports on the presence of type I IFN during the acute phase of HAV infections are controversial. Some indicate that patients do not produce IFN[182-184], while in other reports evidence for the presence of IFN is announced[185-187].

At the cellular level, HAV infections result in a persistent noncytopathic infection[9,188,189] and neither measurable IFN-α/β levels[9,190] nor interference with the infection by other viruses[190] could be detected in lymphocytes and fibroblasts infected with HAV. Further investigations showed that HAV does inhibit IFN-β transcription[191] by effectively blocking IRF-3 activation[192], presumably due to a cooperative effect of the HAV proteins 2B and 3ABC[193] (Figure 2). While MAVS is targeted for HAV protease 3C-mediated proteolysis by 3ABC, an intermediate product of HAV polyprotein processing localized to mitochondria by 3A[194], 2B seems to interfere with MAVS as well as with the kinases IKKε/TBK1 by a so far unknown mechanism[193]. It is assumed that the effects of 2B on MAVS and the kinases indirectly result from interactions of 2B with cellular membrane structures. It could also be demonstrated that HAV is able to affect the TLR3 transduction pathway by direct interaction with TRIF[192] (Figure 2).

These results strongly suggest that IFN-β does not play a role in preventing HAV infections, and that the ability of HAV to interfere with the RIG-I/MDA-5 signaling pathway allows this slowly replicating virus to establish infection. Furthermore, this strategy of inhibiting IRF-3 activation through interference with MAVS and the kinases may allow HAV to preserve the infection for a longer time by preventing IRF-3-mediated down-regulation of the liver cell metabolism[195], and by evading the cellular IFN response at later stages of infection, a time point when RIG-I/MDA-5 may be upregulated by IFN-γ secreted by HAV-specific CTLs (see "Adaptive Immune Response"), enhancing cell responsiveness to viral RNA[196,197].

HAV also has the ability to prevent apoptosis induced by accumulating dsRNA[191], but the underlying mechanism is not clear. It was found that HAV enhances activation of the transcription factor NF-κB[192], and as this pleiotropic factor is involved in expression of anti-apoptotic genes[198], the ability of HAV to activate NF-κB might play a role in the inhibition of apoptosis.

A transient suppression of hematopoiesis with granulocytopenia is frequently observed in the preicteric phase of HAV infections[199,200], and in studies with long-term human bone marrow cultures, HAV-induced inhibition of hematopoiesis was demonstrated[201-203]. As shown with human peripheral blood monocytes, inhibition of the differentiation of monocytes to macrophages by HAV may be involved in the perturbations of hematopoiesis[204]. This might result in an attenuation and retardation of the inflammatory response and of the induction of the adaptive immune response against HAV. The mechanism of this effect is not known. The importance of NK cells for the elimination of HAV is controversially discussed[110,205,206].

CONCLUSION

The data presented here give an overview of the immune responses against PV, coxsackievirus, human rhinovirus and HAV, which are the four best-studied members of the picornavirus family. They illustrate that much is known about the defense mechanisms of the human host against infection with these viruses and about the viral countermeasures, but also that many open questions exist. The immune responses against these viruses, like against other viruses, are complex and as diverse as the viruses themselves.

Processes which are demonstrated for a particular virus do not necessarily also apply to an other virus of this family, not even to a different strain of the same virus. In many cases the viruses were not examined under the same conditions and circumstances. But there may also be similarities between the different viruses which have not been investigated or clearly shown so far. It becomes evident that the time points at which certain responses occur during an infection are very variable and seem to depend on the tissue/cell type infected as well as on individual physiological conditions of the patient, like age or immune status.

Although investigated for many years, some data are incomplete, like type and duration of the antibody responses. The significance of some findings is not clear, as they were obtained using animal models or cultivated cell lines, which do not represent the natural targets for the viruses. For some observations and findings, the mechanisms involved are unknown. For example, it is not totally clear which intracellular receptors are involved in the sensing of picornaviral infections, which signaling path-

ways are involved in cytokine production or mediate the effects of the cytokines, and which signaling pathways are involved in the induction of the expression of cellular receptors participating in the regulation of the immune responses. It is not clear which role the innate immunity plays in recovery from acute infection, and whether the viruses are able to persist, at least for a certain time, in patients with immunoglobulin deficiencies as well as in immunocompetent hosts, and if, in which cell type.

It is not only of importance to find out by which abilities and mechanisms the human picornaviruses interfere with the immune system, but also to identify certain pathogenicity factors which allow the viruses to establish and maintain infection, like the picornaviral 3C protease, which inhibits induction of IFN-β by cleavage of RIG-I/MDA-5 signaling components. This knowledge may allow the prediction of interspecies transmissions from animals to humans by certain members of this large, heterogeneous family. The risk of such transmissions resulting in new emerging diseases is evident by recent epidemics caused by viruses like SARS or hemorrhagic fevers.

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