Acute phase protein response to viral infection and vaccination

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ABSTRACT

Organisms respond in multiple ways to microbial infections. Pathogen invasion tipically triggers an inflammatory response where acute phase proteins (APP) have a key role. Pentraxins (PTX) are a family of highly conserved APP that play a part in the host defense against infection. The larger proteins of the family are simply named pentraxins, while c-reactive proteins (CRP) and serum amyloid proteins (SAA, SAP) are known as short pentraxins. Although high APP levels have been broadly associated with bacterial infections, there is a growing body of evidence revealing increased PTX, CRP and SAP expression upon viral infection. Furthermore, CRP, PTX and SAP have shown their potential as diagnostic markers and predictors of disease outcome. Likewise, the measurement of APP levels can be valuable to determine the efficacy of antiviral therapies and vaccines. From the practical point of view, the ability of APP to reduce viral infectivity has been observed in several virus-host models. This has prompted investigation efforts to assess the role of acute phase response proteins as immunoregulatory molecules and their potential as therapeutic reagents. This work aims to present an overview of the APP response to viral infections reviewing the current knowledge in the field.

1. Pentraxins, c-reactive proteins and serum amyloid proteins. The basics

Living organisms have to be prepared to face external aggressions such as injuries or pathogen invasions. One of the arms of the host defensive response is the activation of the so called acute phase response (APR) that includes the production of inflammatory cytokines and a number of proteins such as c-reactive proteins (CRPs), serum amyloid proteins (SAA, SAP) and pentraxins (PTX). Those are collectively termed acute phase proteins (APP). APP are present in all animal groups studied, from arthropods to vertebrates [1,2]. Nonetheless, most of the research on APP has been conducted on mammalian models.

CRP are classified into the short pentraxins group. They were identified as proteins around 25-kDa synthesized in the liver. CRP blood levels rise notably in patients undergoing inflammatory response to a number of disease conditions, including cancer [3,4]. Human CRP tends to form pentameric structures [1]. It is currently accepted that the balance between monomeric CRP and pentameric CRP states determines its functionality [5–7].

Serum amyloid A (SAA) and serum amyloid P (SAP) are also released to circulation in correlation with antimicrobial and anti-inflammatory activity [8,9]. Both proteins are often found in amyloid deposits such as in atherosclerosis disease [10,11]. CRP and SAP are known to interact with the complement component C1q which results

in the activation of the complement cascade [12].

PTX are larger proteins ($\approx$ 40-kDa) that form multimeric structures [3,13]. PTX production by various cell types is stimulated by microbial infection [14]. PTX are normally stored in blood cells such as neutrophils ready to be released after challenge with the bacterial or viral pathogen [15]. Pentraxin 3 (PTX3) is regarded as the most prominent member of the pentraxin superfamily, with dramatic increase in blood levels upon bacterial and viral infections [13,16]. PTX3 is involved in a number of functions in immunity and inflammation [17].

Several aspects of the APP regarding to inflammation-related disorders have been reviewed by others [3,11,13,18,19]. Here the focus will be set on the response to invading viruses, discussing how the presence of APP in blood and other specific tissues may be altered after viral infection, in association with an enhancement of the host innate immune response. The differential modulation of CRP, PTX and SAP upon microbial challenge makes those proteins ideal markers for disease prognosis and discrimination between bacterial and viral etiology. Furthermore, changes in APP expression after the administration of antiviral drugs and vaccines have been observed, suggesting the possible use of APP as reporters of the efficacy of antiviral treatments.

2. APP response to viral infection

There is a whole body of work dealing with the altered APP profiles

Table 1
APP induced by viral infection.

Virus	APP	host	antiviral action	Ref
Influenza A (IAV)	CRP	human	complement, phagocytosis	[20]
		human	–	[21–24]
		mouse	–	[25]
	SAA	ferret	–	[26]
		mouse	–	[27]
	PTX3	human	binding to virus particle	[28]
		Human	–	[29]
		mouse	binding to virus particle	[30,31]
Swine influenza (SIV)	CRP, SAA	pig	–	[32,33]
	PTX3	pig	–	[106]
Equine influenza (EIV)	SAA	horse	–	[34]
Porcine reproductive and respiratory (PRRSV)	CRP	pig	–	[107]
	SAA	pig	virus enhancer	[35]
Bovine respiratory syncytial (BRSV)	SAA	cattle	–	[36,37]
Hepatitis B (HBV)	CRP	human	–	[38,39]
Hepatitis C (HCV)	CRP	human	–	[40]
	PTX3	human	–	[41]
Murine hepatitis (MHV)	PTX3	mouse	binding to virus particle	[42]
Human immunodeficiency (HIV)	CRP	human	–	[43–45]
Feline immunodeficiency (FIV)	SAA	cat	–	[46]
Pseudorabies (PRV)	CRP	mouse	–	[47]
Dengue (DENV)	CRP	human	–	[48,49]
	PTX3	human	–	[50]
Chikungunya (CHIKV), Ross River (RRV)	PTX3	mouse	binding to virus particle (enhancer)	[14]
Puumala hantavirus (PUUV)	PTX3	human	–	[51,52]
Avian influenza	SAA	chicken	–	[53]
Infectious bursal disease (IBDV)	PTX3	chicken	–	[54]
Spring viremia of carp (SVCV)	CRP	zebrafish	binding to cell (lipid rafts?)	[55,56]

in virus-infected organisms. Representative examples of APP modulation during virus infection have been summarized in Table 1.

2.1. Influenza and other respiratory viruses

Consistent correlations between disease progression and elevated levels of APP have been reported In viral diseases affecting the respiratory tract. Increased APP concentrations in serum of organisms infected with viruses causing respiratory illness can reach the hundreds-thousand-fold over healthy samples [27]. Increased levels of CRP have been found in patients infected with the most virulent types of influenza A virus. Thus, human influenza disease outcome has been associated with enhanced production of CRP, with the highest CRP levels correlating with the more severe symptoms and even mortality [20,21,24]. CRP induction may vary amongst different avian influenza A virus subtypes: H7N9 is a more powerful inductor of CRP and cytokine production than the H1N1 subtype [23]. In fact, the highly pathogenic influenza A H7N9 subtype induces high serum levels of CRP that are associated with a fatal clinical outcome [22].

PTX3 has shown good correlation with the duration of fever in children with respiratory tract infection [29], although it does not seem that PTX3 by its own could be regarded as a good reference for confirming a viral cause. In a recent study, a combined data analysis of CRP, SAA and PTX3 became the best predictor of severe respiratory disease in hospitalized children [57].

In influenza virus infected mice SAA concentration in serum rises several-hundred fold in three days [27]. In other species changes in acute phase protein levels are not so dramatic: CRP and SAA increments of 3-fold and 20-fold, respectively, have been reported in pigs infected with swine influenza [33,58]. Overall, there is a good correlation between severity of disease and CRP serum concentrations after infection with swine influenza virus [58]. SAA was demonstrated to be a useful reporter of disease development in pigs co-infected with viral and bacterial pathogens [59]. In particular, SAA serum levels appear to be the best indicators of disease progression in swine influenza cases [32].

The infection of the respiratory tract may trigger the up-regulation of APP expression in lungs and bronchi. Such extrahepatic upregulation of SAA has also been reported in porcine reproductive and respiratory syndrome virus (PRRSV)-infected pig, particularly in the lungs [35]. Infection with pandemic influenza viruses causes increased levels of SAA in other non-human hosts [26]. SAA plays a part in the host response to equine influenza, with SAA concentrations peaking during the acute phase of the disease [34], in good correlation with the appearance of clinical signs. This observation can be applied to veterinary practice where elevated concentrations of SAA may serve as a marker of respiratory viral infection in cattle [36,37].

2.2. Persistent and latent viral infections

A phenomenon termed *acute* phase response would be expected to develop in a different fashion in long term viral diseases compared to acute viral infections. Hepatitis are amongst the most prevalent chronic viral infections in humans. Hepatitis B and C viruses target the liver, that is the main producer of CRP and serum amyloid proteins as discussed above [60]. Thus, it is not surprising that patients undergoing chronic hepatitis C infection showed higher levels of CRPs than healthy individuals [40]. Similarly, high levels of CRP have been reported in chronic hepatitis B patients in association to liver damage [38,39]. In fact, CRP is considered to be a useful predictor of mortality in hepatitis B infected individuals suffering from cirrhosis [61]. In the same way, elevated plasma levels of PTX3 are considered to be a risk factor of developing liver carcinoma in HCV patients [41].

Retroviruses such as human immunodeficiency virus (HIV) have a well-known capacity for establishing long lasting infections in the body [62]. HIV-exposed infants show elevated CRP levels and other inflammatory markers like interleukin 6 (il6) [44]. A persistently high level of CRP in patients receiving antiretroviral therapy is associated with disease progression and a higher probability of clinical failure [43,45]. This up-regulation of APP upon retrovirus infection has been reported in other species as well. In feline immunodeficiency virus (FIV)-infected cats determination of SAP concentrations in plasma is complementary to the measurements of viral RNA levels when predicting disease progression [46].

Many viruses are known to persist in the host's nervous system

Table 2
Acute phase proteins induced by antiviral vaccines.

vaccine	CRP/PTX	host	ref
Influenza A	CRP	mouse	[25]
Swine influenza	CRP, SAA	pig	[59]
Canine distemper & canine parvovirus	CRP	dog	[73]
Varicella-zoster	CRP	human	[74]
Hepatitis B	CRP	rabbit	[75]
Newcastle disease & avian bronchitis	SAA	chicken	[76]

where they establish a latent infection. Aujeszky's disease (pseudorabies) is a pathology of pigs caused by a herpes virus resulting in neurological signs that can be fatal [63]. The clinical outcome of pseudorabies virus infection in a mouse model is determined by the acute inflammatory response after infection, with high levels of CRP and il6 produced in several tissues [47].

2.3. Other viral infections

A number of systemic infections are caused by arthropod-borne viruses with significant impact on human health. In severe hemorrhagic cases of dengue CRP levels are elevated as well as some inflammatory cytokines including il6 [48,49,64]. However, other authors refer to PTX3 as a more reliable indicator of dengue disease severity [50]. The inflammatory response after chikungunya virus (CHIKV) infection is associated to higher amounts of PTX3 in patients [18]. In acute infections with rodent-borne hantaviruses, disease severity and duration of hospital stays can be inferred from high plasma levels of PTX3 and the appearance of hemorrhagic fever symptoms [51,52].

2.4. Avian and fish viruses

Like mammals, birds possess an innate immune system as the first barrier of defense against pathogens [65]. Therefore, birds are capable of mounting a rapid response upon viral infection [66]. The magnitude of the response may vary among species: avian H5N1 influenza virus causes a rapid elevation of SAA levels in chicken but not in ducks [53], which may explain the lesser mortality rates and less severe disease in ducks compared to chicken. Other viral pathogens of birds can also change APP patterns, like infectious bursal disease virus (IBDV) inducing a 20-fold increase change of PTX3 in infected chickens [54]. The previous reports suggest that APP response to viral challenge is common in poultry.

With a more primitive adaptive immunity, fish are considered to rely heavily on the innate immune response. In fact, some of the APP like CRP are multigene families in fish [67]. Although our current knowledge of APP role in fish viral diseases is still limited, the relevance of CRP and SAA in various antimicrobial defense functions has been recognized [4,68]. Two important viruses affecting fish farming, viral hemorrhagic septicemia virus (VHSV) and spring viremia of carp virus (SVCV) have been shown to alter *crp* gene expression in zebrafish where significant up-regulation of mRNA expression of crp gene isoforms has been observed in zebrafish 2 days after infection with VHSV and SVCV [55]. In parallel, the transcriptional activation of crp gene promoters by histone methylation was shown to increase from day 1 to day 5 post-infection with SVCV [69]. At the protein level, proteomic analysis of blood from SVCV-infected zebrafish revealed a peak of isoforms crp2 and crp5 expression at 24 hpi, returning rapidly to basal levels [55]. A similar response has been observed in carp infected with the herpesvirus CyHV, with a peak of serum concentrations of CRP already at 24 hpi that declined after day 5 [70].

Rock bream SAP profiles are also modulated after iridovirus infection with a peak of SAP levels in the liver of infected fish detected at 3 days post-infection [71,72]. Taken together, the aforementioned findings highlight the involvement of APP in a rapid antiviral response in teleost fish.

The use of APP as therapeutic agents in fish is an attractive possibility supported by some experimental evidence. CRP and SAP have the potential to become wide range antimicrobial compounds, due to their ability to restrict bacterial and viral replication [55,68]. The intraperitoneal administration of recombinant SAP has been shown to protect carp from iridovirus disease [68]. Whether the cost-efficacy of the therapeutic use of recombinant APP would meet the requirements of the fish farming industry is a matter of debate.

3. APP response to vaccination

The administration of antiviral vaccines can induce changes in the profile of pentraxins (Table 2), but often the magnitude of the response is smaller than the response to the corresponding virus infection. That is the case of the influenza virus vaccine where CRP response to vaccination is normally weak [77]. Nevertheless, a number of studies have explored the potential of measuring the changes in APP levels to assess the protective efficacy of a given vaccine. On this respect, it is important to note that the correlation between CRP levels and the efficacy of the vaccine may vary depending on host conditions, particularly age. Elder patients respond to herpes zoster vaccination with lower levels of CRP, which has been taken as an indication of vaccine failure [74]. A similar age-dependent behavior occurs in HIV-infected patients where inflammatory markers correlation with mortality is different among infants and adults [44]. Serum concentrations of CRP during HIV infection can be associated with viral loads and therefore with the efficacy of a therapeutic vaccine [78]. A similar situation is observed in non-human species: the CRP response of mice to influenza virus vaccination is also affected by age, with neonatal mice showing higher CRP levels than adult individuals [25].

Adjuvants are substances added to vaccines to boost the host immune response. Thus, adjuvants may become important factors influencing the APP response to vaccination. In rabbits, the responses associated with acute phase proteins can be either positive or negative depending of the vaccine/adjuvant combination [79]. In fact, some adjuvant formulations by their own can lead to a rapid increase of CRP levels (that later return to basal levels) after injection, which is considered a sign of acute inflammation caused by vaccination [75]. Similar situations have been reported in veterinary preventive care studies. A commercial vaccine against two viral diseases of dogs (Nobivac®) induced only a 2-fold increase in serum levels of CRP [73] that went in parallel to increasing antibody titers against canine distemper virus and canine parvovirus. The work of Romiszewski and colleagues suggested that CRP profiles could be a reliable measure of the efficacy of vaccines for dogs.

Regarding non-mammalian hosts, SAA has been proposed as a candidate marker of vaccine efficacy in poultry. Chickens vaccinated against Newcastle disease virus showed SAA increased ≈3-fold in correlation with higher antibody titers [76].

4. The antiviral activity of APPs

At present it is widely recognized the capacity of APP to limit viral replication and spread within the host, functioning as part of an early defense response before the induction of a specific antibody response against the pathogen. The several ways APP could affect viral replication are discussed in the following sections.

4.1. Direct inhibition through binding to the virus particle

The mechanism of action most widely reported for the antiviral activity of APP is based on their capacity to attach to the virus particles and subsequently block virus-cell interaction. Human PTX3 and SAP binding to influenza virus inhibits virus-induced hemagglutination

[30]. Interestingly, PTX3 and SAP can bind to virus-infected cells but not to uninfected cells, which suggest a selective effect of PTX and SAP during viral infection [28]. By analyzing influenza A virus mutants resistant to the inhibitory effect of PTX3, the amino acid residues in the hemagglutinin (HA) responsible of the virus sensitivity to PTX3 were identified [31], providing further evidence of the recognition of HA by PTX3 in mice. Treatment of influenza virus-infected mice with human PTX3 has been successful in reducing viral loads and increasing survival on the infected animals [30], hinting the potential therapeutic application of pentraxins. In recent years the use of recombinant PTX as antiviral drugs has emerged as a distinct possibility. On this respect, Han and colleagues demonstrated the protective effect of intranasal administration of recombinant PTX3 against murine coronavirus [42]. In the aforementioned study the gene knockout technology was applied to the investigation of the antiviral response of pentraxins, showing higher susceptibility to mouse hepatitis coronavirus MHV in PTX3-deficient mice [42]. Moreover, the observation that PTX3 could bind MHV particles *in vitro* prompted an *in vivo* study where mice were treated with recombinant PTX3, achieving a better clearance of the virus in the lung.

SAP binding to influenza virus HA results in the inhibition of infection in mice, with higher survival observed after intranasal administration of SAP [80]. Likewise the anti-hepatitis activity of SAA is associated with its inhibitory effect on the HCV entry through binding of SAA to the virus particles [81]. A follow up study corroborated that SAA protected cells from HCV infection, blocking a step prior to virus entry into the cell [82]. It is worth to mention that the binding of APP to the virus particle does not always end up with the inhibition of viral replication. On the contrary, PTX3 binding to Ross River virus seems to facilitate virus entry into the cell [14]. Another instance of a "pro-viral" action of APP, porcine SAA has been reported to have an enhancing effect on PRRSV replication *in vitro* [35]. Why pentraxins can both inhibit and enhance viral replication is not fully understood. While the *in vitro* antiviral effects of pentraxins are often related to their virus binding capacity, the *in vivo* effect of APP on viral infectivity is usually mediated by the activation if the innate immune system and interferon pathways [83]. That can lead to a discrepancy between *in vitro* and *in vivo* roles of pentraxins.

4.2. Binding of CRP to cell membranes and induction of autophagy

Binding of CRP to the cell membrane can impair subsequent virus attachment and entry into the cell. The binding seems to be dependent on the affinity of CRP for cholesterol-rich lipid rafts on the cell membrane [6]. That would explain the antiviral activity of zebrafish CRP against SVCV [56]. Human CRP binds rapidly to activated monocytes in a calcium-dependent way, but such binding does not last long: CRP quickly detaches and the cells go back to basal condition [5].

The antiviral action of APP can be also linked to the activation of autophagy. Autophagy is a defensive mechanism of the cell that allows the removal of intracellular microbial pathogens [84]. Disruption of the cell membrane by CRP would trigger the formation of the autophagic vesicles as part of the cell defense mechanism [85,86]. Evidence of the relationship between up-regulation of CRP and autophagy has been reported. In renal cell carcinoma there is a correlation between expression of CRP and ATG9B, a protein involved in autophagy [87]. At present there are some research gaps on the relationship between CRP and autophagy in virus-infected cells that will have to be addressed in the future.

4.3. Modulation of the innate immune response by APP

The innate immune system serves as a rapid first wave of defense against invading pathogens [86]. The immunomodulatory role of APP and their interaction with innate immune cells has been reported [14,88]. Human CRP interferes with the migration of macrophages,

raising the suggestion that CRP may assist to recruit macrophages in the site of tissue injury [89]. Monomeric CRP binding to lipid rafts stimulates production of pro-inflammatory cytokines [6,56]. Likewise, CRP binding to cell membranes also activates the complement cascade through C1q [5].

Serum amyloid proteins also have a regulatory activity on innate immunity and inflammatory cytokines as well [90]. Production of SAA in the liver has a triggering effect on the cytokine response to microbial infections, although its antiviral activity seems to be restricted to HCV [8]. As discussed earlier, a close connection between il6 expression and CRP production has been established in fish and mammals [15,55,91].

5. APP as biomarkers of antiviral treatment efficacy

The measurements of circulating levels of cytokines and APP as well as the characterization of patterns associated to each specific disease condition have been regarded as very useful tools to assist diagnosis of infectious diseases differentiating bacterial from viral origin of the disease [15,92,93]. Particularly, measurements of serum CRP levels have been recommended to distinguish between bacterial and viral diseases [94,95] in those pathologies resulting in febrile condition in children [96]. Immunoassay tests for myxovirus A (MxA) and CRP were the bases of a clinical diagnostic protocol to determine the bacterial or viral etiology of acute respiratory infections [97]. Higher blood levels of CRP can be used to differentiate between bacterial and viral gastrointestinal infection [98,99] and therefore avoiding unnecessary antibiotic therapy. Combined high levels of both CRP and SAA are indicative of bacterial infection in cases on infectious mononucleosis, while elevated SAA (only) points to a viral infection [100]. In addition to the identification of a bacterial or viral origin of a disease the determination of CRP concentrations has been shown to distinguish between viral (dengue) and protozoan (malaria)-infected patients with very similar clinical signs [101].

In a rare case of APP analysis applied to the differential diagnostic of two viruses in a respiratory infection, the analysis of CRP profiles has contributed to validate a diagnostic of influenza virus infection, ruling out rhinovirus infection [102].

Several studies have stressed the utility of APP as biomarkers of disease. Consequently, the determination of APP levels in virus-infected patients has been established as an instrument to evaluate the efficacy of antiviral drugs. For instance, reduced CRP levels are good indicators of the efficacy of interferon-ribavirin combined therapy in HCV-infected patients [40]. SAA and CRP concentrations are elevated in cats receiving interferon therapy against feline immunodeficiency virus and feline leukemia virus. In that model SAA/CRP levels can be taken as evidence of the innate immune system being activated by the antiviral treatment [103]. In mice, on the other hand, lower levels of SAA in serum are associated with the inhibition of influenza virus replication in oseltamivir-treated individuals [27].

Due to their rapid increase after infection, high CRP levels can be used as an early marker of viral disease in fish, before the outcome of the symptoms. However, they could not be used for differential diagnosis, since both viral and bacterial infections induce the upregulation of crp expression in fish [68,72,104,105].

6. Conclusions

Despite the intensive research conducted on APP in the past decade we are only beginning to understand all the functions played by APP in virus-infected organisms. It is now evident that APP are key components of the antimicrobial response, very often involved directly or indirectly in the inhibition of viral replication and spread within the host. We have managed to get some insight into their range of antiviral activities but many open questions remain: is the APP stimulation sufficient to provide a primary protection against viral pathogenesis? Can the innate immune system be "trained" to keep a memory of the

APP response? Thus, active research is needed to assess the full potential of APP as therapeutic agents for viral diseases as well as biomarkers of the efficacy of antiviral treatments.

Several final conclusions can be drawn from the body of knowledge in the field:

1 CRP expression is up-regulated in a broad range of human virus infections.
2 In non-human hosts serum amyloid proteins (SAA, SAP) are the main APP altered after viral infection.
3 CRP are the most widely upregulated APP upon antiviral vaccination.
4 The antiviral activity of APP *in vitro* is associated with their virus-binding capacity.
5 APP use as diagnostic tools is largely dependent on the virus-host situation.

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