Allergo J Int 2018; 27: 79–96

Respiratory virus-induced heterologous immunity

Part of the problem or part of the solution?

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Keywords
respiratory virus – cross-reactivity – adaptive immunity – autoimmunity – asthma

Abstract

Purpose: To provide current knowledge on respiratory virus-induced heterologous immunity (HI) with a focus on humoral and cellular cross-reactivity. Adaptive heterologous immune responses have broad implications on infection, autoimmunity, allergy and transplant immunology. A better understanding of the mechanisms involved might ultimately open up possibilities for disease prevention, for example by vaccination.

Methods: A structured literature search was performed using Medline and PubMed to provide an overview of the current knowledge on respiratory-virus induced adaptive HI.

Results: In HI the immune response towards one antigen results in an alteration of the immune response towards a second antigen. We provide an overview of respiratory virus-induced HI, including viruses such as respiratory syncytial virus (RSV), rhinovirus (RV), coronavirus (CoV) and influenza virus (IV). We discuss T cell receptor (TCR) and humoral cross-reactivity as mechanisms of HI involving those respiratory viruses. Topics covered include HI between respiratory viruses as well as between respiratory viruses and other pathogens. Newly developed vaccines, which have the potential to provide protection against multiple virus strains are also discussed. Furthermore, respiratory viruses have been implicated in the development of autoimmune diseases, such as narcolepsy, Guillain-Barré syndrome, type 1 diabetes or myocarditis. Finally, we discuss the role of respiratory viruses in asthma and the hygiene hypothesis, and review our recent findings on HI between IV and allergens, which leads to protection from experimental asthma.

Conclusion: Respiratory-virus induced HI may have protective but also detrimental effects on the host. Respiratory viral infections contribute to asthma or autoimmune disease development, but on the other hand, a lack of microbial encounter is associated with an increasing number of allergic as well as autoimmune diseases. Future research might help identify the elements which determine a protective or detrimental outcome in HI-based mechanisms.

Cite this as Pusch E, Renz H, Skevaki C. Respiratory virus-induced heterologous immunity – Part of the problem or part of the solution? Allergo J Int 2018; 27:79–96
https://doi.org/10.1007/s40629-018-0056-0

Submitted
December 20, 2017

Accepted
February 15, 2018

Online-Version
http://link.springer.com/journal/40629

Literraturreferat
dieser Arbeit auf Deutsch: Seite 12

Introduction

Respiratory viruses, such as respiratory syncytial virus (RSV), rhinovirus (RV) and influenza virus (IV) frequently cause upper (URTI) and lower respiratory tract infections (LRTI). Such infections include the common cold, pneumonia, bronchitis and bronchiolitis.

Direct and indirect costs associated with viral respiratory tract infections other than IV add up to $40 billion annually in the USA [1]. The annual burden due to IV epidemics is estimated to be around $87 billion in the USA [2]. Seasonal IV epidemics affect about 1 billion of the global population and cause up to half a million deaths every year (WHO). A viral aetiology is found in ~70 % [3] of all common cold cases, while RV alone accounts for ~50 % [3]. Furthermore, RV was detected in 9 % of patients hospitalized for severe community-acquired pneumonia, i.e. more often than IV (6 %) or *Streptococcus pneumoniae* (5 %) in the same study [4].

Especially children, adults > 65 years of age and the chronically ill are at high risk of developing severe disease upon LRTI. Acute LRTI are one of the major causes of childhood mortality worldwide [5]. RSV and IV are among the main pathogens causing acute LRTI in children under 5 years with at least 53 million cases of acute- and 4,4 million cases of severe acute LRTI annually [6, 7].

Viral RTI, especially RV infection, frequently cause chronic obstructive pulmonary disease (COPD) [8] and asthma [9] exacerbations. Respiratory viruses have also been implicated in the development and persistence of asthma [9, 10] as well as the initiation of autoimmune disease [11]. Despite the large impact on society, treatment of these viral infections is mostly supportive.

We discuss respiratory virus-induced adaptive heterologous immune mechanisms in infections, autoimmunity and asthma. Specifically, we describe published data in the involved virus strains, implicated T/B cell epitopes and final outcome among others. A better understanding of heterologous immunity (HI) potentially leads to new therapeutic or preventive strategies for a range of immunologically mediated disorders.

Abbreviations

ACTH	Adrenocorticotropin
Ad	Adenoviruses
ADEM	Acute disseminated encephalomyelitis
APC	Antigen presenting cell
BRSV	Bovine RSV
CD	Celiac disease
CMV	Cytomegalovirus
COBRA	Computationally optimized broadly reactive antigen
COPD	Chronic obstructive pulmonary disease
CoV	Coronavirus
CV	Coxsackie virus
EAE	Experimental autoimmune encephalomyelitis
EBV	Epstein–Barr virus
F	Fusion protein
Fab	Fragment antigen binding
G	Attachment glycoprotein
GBS	Guillain–Barré syndrome
GM3	Monosialodihexosylganglioside
HCV	Hepatitis C virus
HCV-SN	HCV seronegative
HDM	House dust mite
HI	Heterologous immunity
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HMPV	Human metapneumovirus
HPV	Human papilloma viruses
IFN	Interferon
IL	Interleukin
IM	Infectious mononucleosis
IV	Influenza virus
kDa	Kilodalton
LAIV	Live attenuated influenza vaccine
LRTI	Lower respiratory tract infections
mAb	Monoclonal antibody
MBP	Myelin basic protein
MERS	Middle East respiratory syndrome
MHC	Major histocompatibility complex
MOG	Myelin oligodendrocyte protein
MYHC	Myosin heavy chain
NKT	Natural killer T cell
NMDAR	Anti-N-methyl-D-aspartate receptor
OVA	Ovalbumin
pMHC	peptide-MHC
rRBD	Recombinant receptor binding-domain
RSV	Respiratory syncytial virus
RTI	Respiratory tract infections
RV	Rhinovirus
S	Spike protein
SARS	Severe acute respiratory syndrome
SLE	Systemic lupus erythematosus
SS	Sjögren's syndrome
T1DM	Type 1 diabetes mellitus
TCR	T cell receptor
T_{em}	T effector memory cells
TLR2	Toll-like receptor 2
T_m	T memory
TRIB2	Tribbles homolog 2
T_{rm}	Tissue resident memory
URTI	Upper respiratory tract infections
VP	Viral capsid proteins

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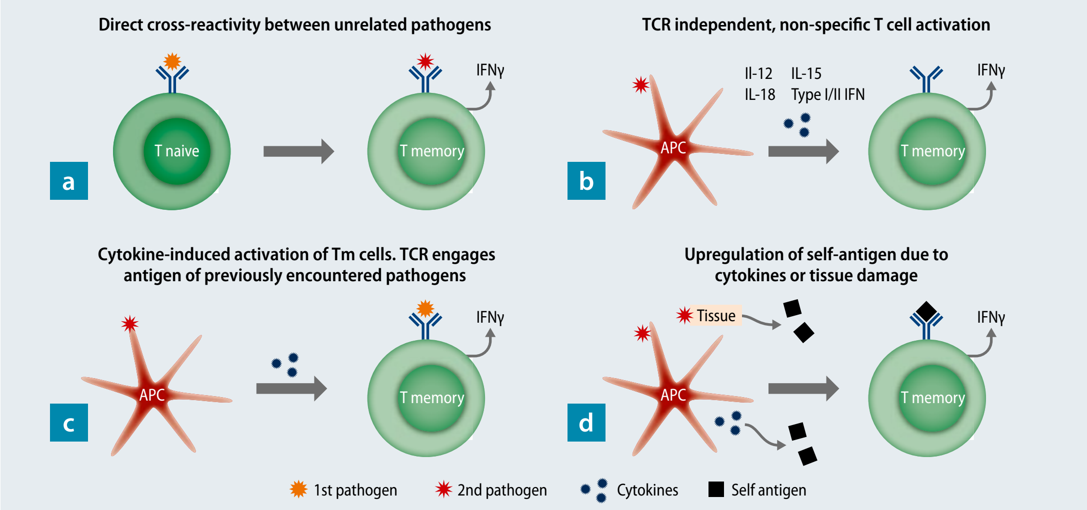
Heterologous Immunity

HI is the altered immune response towards an antigen as a result of a preceding encounter with an unrelated antigen. Thus, immune memory is a central requirement for HI. Therefore, heterologous immune responses have exclusively been linked to the adaptive immune system. However, in recent years, innate immune memory has been described [12] and some vaccines have been associated with substantial innate heterologous effects [13]. Heterologous innate immune stimulation is a way to alter adaptive immune responses towards an antigen. This involves the induction of tolerance, Th polarization, substitution, breaking of tolerance or enhancement of adaptive immune cell responses, while maintaining antigen specificity (see **Fig. 3**) [14].

Both, B and T cells have been shown to mediate heterologous effects. Antibodies have been shown to protect from heterologous virus challenge [15]. On the other hand, antibodies induced by viral infection contribute to autoimmune disease [11] and possibly play a role in alloreactivity [16]. Evidence suggests that T cell receptor (TCR) cross-reactivity is common between respiratory viruses [17, 18, 19, 20], but it has also been shown between unrelated viruses [21, 22, 23] and even between viruses and other microbial species [23]. Cross-reactive T cells were shown to protect from heterologous virus challenge [18, 20]. Furthermore, pathogen-derived mimics of a tumor-associated antigen are able to enhance the T cell response towards the tumor antigen [24]. Therefore, pathogen-derived epitopes might be used in a tumor vaccine. HI also has detrimental effects on the host. For example, pre-existing T memory (T_m) cells can restrict the priming of protective naïve T cells to heterologous antigen [25]. Furthermore, pre-existing T_m cells can narrow the primary T cell response by shifting towards proliferation of high affinity clones only [26]. A narrowed T cell response may lead to escape variants and has been shown to be associated with severe disease progression [27, 28]. Furthermore, virus-mediated TCR cross-reactivity has also been shown to involve allo- [16] as well as autoantigens [11, 29]. Cross-reactive $CD8^+$ T cells contributed to transplant rejection in many [16], although not all cases [30].

Unspecific activation of T_m cells has also been associated with HI in some settings. Different mechanisms have been suggested for unspecific T cell activation, e.g. IL-15 [31], IL-12 and IL-18 [32], type I interferons (IFN) [33] and type II IFN [34] signalling (**Fig.1**). Bystander activated T_m cells can contribute to early pathogen control [32, 35]. Tissue resident memory (T_{rm}) cells have an important role in pathogen clearance in the lungs. Since T_{rm} stay at the site of infection after pathogen clearance, they provide rapid protection upon homologous virus challenge in mice [36] and humans [37]. Lung T_{rm} were shown to protect from heterosubtypic IV chal-



APC, antigen presenting cell; IL, Interleukin; IFN, Interferon; TCR, T cell receptor; T_{em}, T effector memory cells

Fig. 1: Mechanisms of T cell-mediated heterologous immunity. **a:** Activation of T memory cells by heterologous pathogens may occur via TCR cross-reactivity. **b:** or via cytokine-induced unspecific (bystander) activation without TCR engagement. **c:** In addition, cytokine-induced activation of Tm cells by the second pathogen may lead to TCR recognition of residual antigen of the first pathogen. **d:** Finally, virus-induced cytokines or tissue damage may release self antigen, which is recognized by the TCRs of Tm cells. (Adapted from Welsh et al. [28].)

lenge in mice [38, 39]. Of note, HI may alter the immunodominance, induce changes in Th polarisation or result in loss of specific T_m cells [28]. In addition, heterologous immune responses are not necessarily reciprocal [40].

Cellular/humoral cross-reactivity

T cells are equipped with TCRs, with whom they sense their cognate antigen. Major histocompatibility complex (MHC) molecules present peptide antigen to T cells in the form of peptide-MHC (pMHC) complexes. MHC I molecules present peptides 8 to 14 mers of length [41]. MHC class II molecules are able to present even longer peptides. The estimated number of divergent TCRs in the human native T cell pool is $< 10^8$ [42], whereas the number of potential foreign peptides presented by MHC molecules is suggested to be $> 10^{15}$ [41]. Taken together, broad TCR cross-reactivity is inevitable for sufficient immune protection [41, 43]. This theory is further supported by the finding that one TCR is able to recognize > 1 million different peptides presented by one MHC molecule [44]. Cross-reactivity is common between peptides with a high degree of sequence homology [23, 45, 46, 47], but also peptides with little homology are able to elicit cross-reactive immune responses [29, 48, 49, 50, 51]. Moreover, TCR cross-reactivity is restricted to peptides of the same length, when presented via MHC class I [52]. Cross-recognition between seemingly non-related peptides might occur due to hotspot binding, where the peptide-TCR interaction is focused on a hotspot, while tolerating substitutions in other positions [53].

B and plasma cells contribute to host protection by producing antibodies, which can neutralize pathogens and/or toxins. The recognition of antigen occurs at the binding cleft of the antibody, which is located in the fragment antigen binding (Fab) domain. The binding cleft contains multiple paratopes, which recognize B cell epitopes on antigens [54]. Therefore, all antibodies are potentially polyspecific [54], which might be necessary to provide sufficient immune protection against the majority of pathogens. B cell epitopes constitute of 15 amino acids on average [55] and most of them are, in contrast to T cell epitopes, conformational or discontinuous epitopes [56]. In addition, hotspot recognition is also likely in antibody-antigen interaction [56].

Heterologous immunity between respiratory viruses

Coronaviruses (CoV)

Middle East respiratory syndrome (MERS)-CoV and severe acute respiratory syndrome (SARS)-CoV caused recurrent epidemics, which were associated with a high mortality. $CD4^+$ and $CD8^+$ T cells as well as antibodies have all been suggested to have protective effects against SARS-CoV infection [57]. Humoral cross-reactivity between SARS- and MERS-CoV was absent in several studies [58]. But recently, Tai et al [59] showed that immunization of mice with recombinant receptor binding-domain (rRBD) of the spike (S) protein from different MERS-CoV strains induced broadly neutralizing antibodies against up to 17 human and camel MERS-CoVs. Intranasal vaccination with a viral vaccine vector, which encodes a conserved SARS-CoV $CD4^+$ T cell epitope protected mice from homologous and heterologous challenge with MERS-CoV. Protection was dependent on cross-reactive $CD4^+$ T cells, producing IFNγ [60].

Influenza virus (IV)

$CD4^+$ and $CD8^+$ T cells generated in a preceding IV infection or vaccination are able to provide protection against heterosubtypic IV infection in humans [18, 20] or mice [17]. T cell cross-strain protection is due to recognition of conserved IV proteins. Seasonal IV vaccines generate strain-specific neutralizing antibodies against HA and NA, but fail to induce a significant cross-reactive response. Therefore, a major goal is to develop IV vaccines, which induce a cross-reactive T cell and/or antibody response.

One target might be the immunodominant human leukocyte antigen(HLA)-A2-$M1_{58}$ epitope, which is conserved over strains for many years, although mutations were detected [47]. Valkenburg et al [47] showed that $M1_{58}$-specific $CD8^+$ T cells also recognized three naturally occurring $M1_{58}$-peptide variants. In addition, $M1_{58}$-specific T_{em} cells from unexposed adults lysed IV A H1N1 2009 pandemic (A(H1N1)pdm09) infected cells *ex vivo* [61]. Therefore, the $M1_{58}$-epitope is a potential target for a broadly IV protective vaccine.

Prime-boost vaccination with the licenced live attenuated influenza vaccine (LAIV) conferred enhanced protection against heterosubtypic IV A challenge compared to FluZone or control. Protection was dependent on $CD4^+$/$CD8^+$ T cells, which also protected against heterosubtypic challenge [62]. In addition, the 2014–2015 and 2015–2016 seasons LAIV vaccine induced lung $CD4^+$ $CD44^+$ CD62Llo $CD69^+$ T_{rm} cells in C57BL/6 mice [39]. Mice were protected against heterosubtypic challenge for up to 45 weeks [39]. LAIV vaccination was also shown to boost pre-existing cross-reactive T cells in 50 % of vaccinated children [63].

Vaccination with self-amplifying mRNA (SAM®) (GlaxoSmithKline, London, UK) in lipid nanoparticles, encoding for conserved internal IV A proteins (nucleoprotein [NP] and/or matrix protein 1 [M1]), induced proliferation of NP- and M1-specific $CD4^+$ Th1 cells as well as $NP_{147-155}$-specific $CD8^+$ T cells in mice. All vaccinated mice survived hetero-

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subtypic IV A challenge [64]. Evidence suggests that innate immune stimulation leads to a broader adaptive immune response [64]. A Toll-like receptor 2 (TLR2)-agonist together with a split IV vaccine, but not vaccine alone, protected mice against homologous and heterologous virus challenge. Heterologous effects were dependent on $CD8^+$ T cells specific for $NP_{147\text{-}155}$ [65].

The HA consists of the highly variable globular head domain, which is the main target of the antibody response, and the stalk/stem domain. The stalk domain is highly conserved among two groups in IV A [66]. Anti-stalk antibodies occur in lower titers and less frequent than anti-head antibodies and are infrequently induced by inactivated IV vaccines [66, 67]. An inactivated H5N1 vaccine showed on average a fourfold anti-stalk antibody increase in humans after the first immunization [67]. Different approaches for a stalk vaccine are under investigation and hold promise for a universal IV vaccine [68].

Computationally optimized broadly reactive antigen (COBRA) vaccines of the HA head domain have the potential to generate broadly protective antibodies. Seasonal and pandemic-derived H1N1 COBRA HAs with the broadest HAI activity were inoculated into mice, using virus-like particles (VLP). Vaccination induced broadly-reactive antibodies and protected mice from A(H1N1)pdm09 challenge [69].

Another approach to overcome strain-specific immunity are vaccines containing the highly conserved extracellular domain of the IV matrix protein 2 (M2e). Many different VLPs are used to enhance the otherwise low immunogenicity of M2e [70]. Different M2e-based vaccines induced anti-M2e antibodies [38, 70], but also $CD4^+$ or $CD8^+$ T cells [71, 72], which were protective against heterologous virus challenges in mice. Furthermore, M2e-VLP-induced lung $CD8^+$ T_{rm} cells, which mediated long lived (> 4 months) heterologous protection in mice [38]. Different M2e-vaccines [70] and an anti-M2e monoclonal antibody (mAb) [73] were safe in human trials, but immunity can still be improved.

Respiratory syncytial virus (RSV)

In response to RSV infection, the anti-fusion (F) protein and anti-attachment glycoprotein (G) are the main antibodies produced [74, 75]. $CD8^+$ T cells contribute to RSV clearance in murine models [74] and lung $CD8^+$ T_{rm} have protective effects in human RSV challenge [37]. No vaccine is currently available against RSV, although many approaches for a broadly protective vaccine have been discussed [74]. Vaccination of mice with a recombinant fusion protein, containing a conserved region of the G $protein_{131–230}$ of RSV-A and RSV-B strains, resulted in IgA and IgG antibodies specific for both RSV-A and RSV-B G proteins. This vaccination protected mice from challenge with RSV-A or RSV-B [76]. The calf animal model is closer to RSV infection in humans. Taylor et al. [77] vaccinated calves with viral vectors expressing sequences of the F, N and M2-1 proteins of human RSV (HRSV). The vaccination induced neutralizing antibodies as well as $CD4^+$ $IFN\gamma^+$ T cells. Calves were protected from heterologous bovine RSV (BRSV) challenge, possibly because of cross-reactivity, since HRSV and BRSV have a high degree of sequence homology. Cross-reactivity of human antibodies has also been detected between two epitopes of the G protein of RSV-A and RSV-B. Such human IgG antibodies showed neutralizing effects against both viruses in HEp-2 cell culture [75]. Furthermore, human mAbs, cross-neutralizing RSV and human metapneumovirus (HMPV), have been identified [15, 78]. One of these mAbs also reacted to two other paramyxoviruses [15], while protective effects upon infection with the aforementioned viruses in murine models have been described [15, 78].

Rhinovirus (RV)

Infection with RV generates serotype-specific antibodies, which can prevent infection with the same serotype. Since there are over 160 distinct RV strains characterized to date [9], reinfection with other strains is common. Viral capsid proteins (VP) of RV contain sequences [79] and T cell epitopes [80], which are conserved across strains. Therefore, humoral or cellular cross-reactivity might provide cross-strain protection against heterologous RV infection.

Immunization with RV-A16-derived VP0 and a Th1 promoting adjuvant protected mice from heterologous RV-A1B challenge [9, 79]. $CD4^+$ Th1 cells were preferentially expanded. Lung T cells from immunized and RV-A1B-infected mice showed increased IFNγ production compared to control, upon stimulation with RV-A16 VP0 and heterologous RV14 and RV-A1B-VP0 peptides. Immunization also enhanced neutralizing antibodies in heterologous RV challenge. Cross-reactive IgG1 VP1-specific antibodies, especially between RV-A and -C, have been detected in humans [81]. Limitations might arise from the fact that some antibodies bind nonprotective epitopes, which might lead to immune escape of RV [82].

Seronegative, healthy humans have $CD4^+$ and $CD8^+$ T cells against RV-A39 epitopes [19]. Co culture of DCs, RV-A39 and T cells resulted in proliferation of $CD4^+$ and $CD8^+$ T cells and enhanced IFNγ production. Muehling et al. [80] showed that pre-existing $CD4^+$ Tm cells, specific to conserved epitopes of the VP region, proliferate upon RV-A16 challenge in seronegative donors. CD4$^+$ T_m cells mainly showed a Th1 or T follicular helper phenotype. Furthermore, RV-A16 $VP2_{162–181}$-specific T cells also recognized the $VP2_{169–188}$ epitope of RV-A39. The results suggest that T_m cells specific for conserved RV regions may mediate heterologous protection. Conserved sequences might be used in a peptide vaccine, which could be especially useful in asthmatics or COPD patients.

Heterologous immunity between respiratory and other viruses

Epstein-Barr virus (EBV)

EBV is the causative pathogen of infectious mononucleosis (IM), the disease severity of which varies substantially. Children usually show mild to no symptoms, whereas adolescents and adults often present with more severe symptoms. Reactivation of IV-$M1_{58}$-specific CD8$^+$ T cells, which are cross-reactive to the EBV BamHI M fragment leftward open reading frame $1_{280–288}$ ($BMLF1_{280}$) epitope were shown to contribute to lymphoproliferation in IM ([48]; **Tab. 1**). In addition, frequency of IV-$M1_{58}$ and $M1_{58}$-EBV $BMLF1_{280}$ tetramer$^+$ CD8$^+$ T cells correlated with IM disease severity [83]. This was associated with different TCR repertoire usage and enhanced IFNγ production. Others found bystander activation, but no expansion of IV-specific CD8$^+$ T cells in IM [84]. $BMLF1_{280}$-specific CD8$^+$ T cells of human donors were shown to recognize up to two IV-derived and two EBV-derived epitopes [49]. Private TCR repertoire usage might explain differences in the number of peptides recognized by $BMLF1_{280}$-specific CD8$^+$ T cells between donors [49]. Recent data suggest that T cell cross-reactivity between IV-$M1_{58}$, and $BMLF1_{280}$ and BamHI R fragment leftward open reading frame $1_{109-117}$ protects some adults from primary EBV infection [85]. Seronegative status was associated with usage of a private oligoclonal TCR repertoire and higher frequency of CD103$^+$ IV-M1-specific T cells. The authors speculate that cross-reactive T_{rm} might prevent primary EBV infection of B cells in the tonsils.

Hepatitis C virus (HCV)

Acute HCV infection is variable in its symptoms, ranging from asymptomatic to severe disease. The HLA-A2 restricted nonstructural protein $3_{1073–1081}$ ($NS3_{1073}$) epitope of HCV is a target for CD8$^+$ T cells in HCV infection. $NS3_{1073}$-specific T cells were detected in the blood of HCV positive donors, but also in HCV seronegative (HCV-SN) donors [22, 86]. Further analysis showed first that $NS3_{1073}$-specific T cells are cross-reactive to the IV-derived $NA_{231-239}$ epitope and second that IV infection induced HCV specific T cells [22]. Another study found the cross-reactivity between those epitopes to be weak and recognition of the $NA_{231–239}$ epitope was dependent on preceding HCV infection [87]. $NS3_{1073}$-reactive T cells were shown to be cross-reactive to cytomegalovirus-(CMV), Epstein-Barr virus(EBV)-derived and the IV $M1_{58}$ epitopes in vitro [86]. Therefore, $NS3_{1073}$-reactive T cells might originate from infection with one of these viruses. Pre-existing cellular immunity towards the $NS3_{1073}$ epitope can either result in an enhanced immunity, as shown in evaluation of a HCV peptide vaccine trial [86], or have detrimental effects, as shown by Urbani et al. ([27]; **Tab. 1**). The latter found that patients with severe HCV liver disease used a private TCR repertoire, with T cells cross-reactive to $NA_{231–239}$ and $NS3_{1073}$ epitopes. In those patients the CD8$^+$ T cell response was narrowly focused on the $NS3_{1073}$ epitope [27].

Adenoviruses (Ad) are known for their potential as viral vectors in vaccination against infection [88] and have also been utilized for gene therapy [89]. Inoculation of Ad serotype 5 (Ad5) into mice induced robust humoral and cellular immunity against multiple HCV peptides in vitro and resulted in enhanced virus clearance [90]. Moreover, HCV-SN donors with pre-existing Ad immunity showed cross-reactive humoral and cellular immunity towards HCV peptides [90]. Further studies are needed to determine the possible use of Ad in the development of a vaccine for HCV. Limitations may arise from pre-existing Ad immunity, which possibly leads to lack of response to vaccination.

Human immunodeficiency virus (HIV)

T cell cross-reactivity was detected for the HLA-A2 restricted IV-$M1_{58}$ and the HIV-1 p17 $GAG_{77–85}$ epitopes in vitro, among both HIV seropositive and seronegative donors ([21]; **Tab. 1**). Cross-reactivity was weak in some seronegative donors, which suggests that a strong T cell response to the IV-$M1_{58}$ is necessary to induce HIV-1 reactive T cells. A larger cohort study with 175 HIV seropositive HLA-A2$^+$ subjects confirmed HIV-1 and IV cross-reactivity. T cells of HIV$^+$ individuals frequently targeted the p17 $GAG_{77–85}$ and the IV-$M1_{58}$ epitopes *in vitro* [51]. About 40 % showed T cells specific for both epitopes *in vitro* [51]. No effect of IV and HIV cross-reactive T cells on the course of HIV infection could be detected.

Adenoviral vectors are used to form an HIV vaccine. To avoid formation of strain specific antibodies, rare adenovirus strains are utilized. Unfortunately, also pre-existing cellular immunity against adenoviral vectors can impede successful vaccination. Frahm et al. [91] showed that pre-existing Ad5-specific CD4$^+$ T cells led to decreased numbers of CD4$^+$ HIV-specific T cells and to a narrowed CD8$^+$ T cell response upon Ad5-based HIV vacci-

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Tab. 1: Heterologous immunity between respiratory and nonrespiratory viruses. Involved proteins and epitopes are listed in connection to a given MHC background. Amino acids in common between two epitopes are indicated in bold.

Allele	Respiratory virus	Respiratory virus epitope	Sequence	Other pathogen	Other epitope	Sequence	Outcome	Ref.
HLA-A2	IV	$M1_{58}$	**G**ILGF**V**FT**L**	EBV	$BMLF1_{280\text{-}288}$	**G**LCTL**V**AM**L**	detrimental	[48, 83]
							beneficial	[85]
		$M1_{58}$	GI**L**GFVFTL	EBV	$BRLF_{109\text{-}117}$	YV**L**DHLIVV	beneficial	[85]
		$NP_{85\text{-}94}$	K**L**GEFYNQMM	EBV	$BMLF1_{280\text{-}288}$	G**L**CTLVAML	–	[49]
		$M1_{58}$	G**I**LGFVF**T**L	HCV	$NS3_{1073\text{-}1081}$	C**I**NGVCW**T**V	beneficial	[86]
		$NA_{231\text{-}239}$	**CVNG**SCF**TV**	HCV	$NS3_{1073\text{-}1081}$	**C**I**NG**VCW**TV**	detrimental	[27]
		$M1_{58}$	GILGF**V**F**TL**	HIV-1	P17 $GAG_{77\text{-}85}$	SLYNT**V**A**TL**	–	[21, 51]
		$HA_{398\text{-}410}$	SVI**EKMNTQ**FTAV	*T. vaginalis*	Hypothetical $protein_{118\text{-}130}$	KMI**EKMNTQ**TEVR	–	[23]
			SVI**EKMNTQ**FTAV	*F. magna*	Hypothetical $protein_{131\text{-}143}$	EKV**EKMNTQ**Y**TA**T	–	[23]
HLA-A2	CoV	$NS2_{52\text{-}60}$	T**MLD**I**QPE**D	HPV 16	$E7_{11\text{-}19/20}$	Y**MLD**L**QPE**T(T)	–	[46]
C57Bl/6 Human	Ad5	–	–	HCV	Various	–	beneficial	[90]

Ad5, Adenovirus serotype 5; BMLF1, BamHI M fragment leftward open reading frame 1; BRLF1, BamHI R fragment leftward open reading frame 1 (both from EBV-derived immediate-early lytic protein); CoV, Coronavirus, E7, Transforming protein E7; F. magna; Finegoldia magna; EBV, Epstein-Barr-Virus; HA, Hemagglutinin; HCV, Hepatitis C Virus; HIV, Human Immunodeficiency Virus; HLA, human leukocyte antigen; HPV 16, Human Papillomavirus type 16; IV, Influenza Virus; M1, Matrix protein 1; NA, Neuraminidase; NP, Nucleoprotein; NS2, Nonstructural protein 2; NS3, Nonstructural protein 3; p17 GAG, group-specific antigen(gag)derived Matrix Protein (p17); T. vaginalis, Trichomonas vaginalis

nation in humans. In addition, extensive T cell cross-reactivity between adenovirus strains was shown. Furthermore, $CD4^+$ HIV-cross-reactive T_m cells have been detected in unexposed adults [23], which further complicates prediction of anti-HIV immunity.

Human papilloma viruses (HPV)

High risk HPVs, such as type 16, 18 and others are the main risk factor for multiple genital cancers. Nilges et al. [46] described cross-reactivity between HLA-A2-binding epitopes $E7_{11\text{-}19/20}$ of HPV type 16 and the $NS2_{52-60}$-derived epitope of human CoV OC43 (**Tab. 1**). HPV E7-reactive $CD8^+$ T cells were found in patients with cervical cancer and even more often in healthy blood donors. $E7_{11-19/20}$-reactive T cells in healthy donors were possibly formed in CoV infection. Whether T cell cross-reactivity here has negative effects on antitumor immunity or might support tumor clearance remains to be determined.

Heterologous immunity between respiratory viruses and pathogens other than viruses

Pre-existing $HA_{391-410}$-specific $CD4^+$ T_m cells showed expansion after seasonal IV vaccination. These T_m cells expanded after stimulation with the *Trichomonas vaginalis* (*T. vaginalis*)-derived hypothetical $protein_{118-130}$- and the *Finegoldia magna* (*F. magna*)-derived hypothetical $protein_{131-143}$ peptide *in vitro* (**Tab. 1**). $HA_{391-410}$-specific $CD4^+$ T cells from one donor recognized both peptides, whereas in the other donor the T cells only recognized the *F. magna* peptide. Furthermore, the two peptides stimulated different IV-reactive T cell clones with distinct affinity [23]. These findings might be a result of first, differential shaping of HI based on encounter with diverse pathogens and second the fact that HI is not necessarily reciprocal.

The oral live-attenuated salmonella typhi Ty21a strain vaccine induced both an increase of Ty21a-reactive and influenza-reactive T cells in the duodenal mucosa of healthy adults [92]. Homing markers were upregulated in Ty21a-reactive and influenza-reactive T cells. More studies are needed to better determine the mechanism behind the increase of influenza-specific T cells in the duodenal mucosa.

Autoimmunity

Acute disseminated encephalomyelitis (ADEM)

ADEM is preceded by either infection in up to 77 % of cases [93] or vaccination in 5–10 % of cases [94]. Episodes of infection or vaccine related ADEM may also occur in the same patient [95]. HMPV [96], parainfluenza [97] and IV infection [98] or IV vaccination [94] preceding ADEM, have all been reported. Influenza infection has been shown to trigger [99] or exacerbate [100] disease in experimental autoimmune encephalomyelitis (EAE) models, which might be a useful to study ADEM [101].

In patients affected by ADEM, myelin basic protein (MBP)-reactive T cells [102] as well as different neuronal antibodies, including anti-myelin oligodendrocyte protein (MOG) have been detected [103]. Generation of these autoreactive T cells and antibodies is probably due to molecular mimicry. TCR cross-reactivity between MBP/MOG-derived and respiratory virus-derived epitopes has been shown for coronavirus [104], adenovirus [29] and influenza A virus HA epitopes ([2950]; **Tab. 2**). Anti-MOG antibodies, which are frequently found in ADEM [103], might have a pathogenic role, since they induce demyelinating disease in EAE animal models [105].

Guillain–Barré syndrome (GBS)

About 60 % of all GBS cases are thought to be infection-related [106], most frequently gastrointestinal or respiratory tract infections including influenza [98]. Molecular mimicry of antibodies against pathogen-derived and self-antigens seem to play a major role in the initiation of GBS [106] and this is best described for *Campylobacter jejuni*.

A recent meta-analysis found a slight, but significant increase in the relative risk of influenza vaccine-associated GBS among 39 studies published between 1981 and 2014 [107]. Others found no such increase in disease risk [106]. The link between influenza infection and subsequent development of GBS is better established [106].

The mechanisms of influenza- and influenza-vaccine-induced GBS largely remain unknown. A first clue might be the findings of Nachamkin et al. [108], who showed that the A/NJ/1976 (H1N1) vaccine as well as trivalent vaccines from 1992–1993 and 2004–2005 seasons induced anti-HA and also anti-GM1 antibodies in mice after immunization. In addition, the 2004–2005 vaccine contains glycolipid-like structures, as shown by positive anti-GM1 immunostaining [108]. Anti-GM-1 antibodies showed a low, but detectable hemagglutination inhibition activity.

Tab. 2: Heterologous immunity between respiratory viruses and autoantigens. Host- and virus-derived proteins as well as epitopes are listed. Amino acids in common between two epitopes are indicated in bold.

Disorder	Respiratory viruses (association)	Immune cells involved	Pathogen-derived protein	Pathogen-derived epitope sequence	Host-derived epitope	Host-derived epitope sequence	Comment	Ref.
ADEM	Ad, HMPV, HPIV, IV infection / vaccination	T cells	IV HA	YRNLVW**F**I**K**KNTRYP	MBP$_{85-99}$	ENPVVH**F**F**K**NIVTPR	–	[29]
			Ad 12 ORF	DFE**VV**T**F**L**K**D**V**LPE		ENP**VV**H**F**F**K**NI**V**TPR		
			IV HA$_{306-318}$	YVKQ**NTL**KLA	MOG	VLIK**NTL**RSL	–	[50]
				YVKQ**N**TL**KL**A		SAAN**N**NI**KL**L		
CD	Ad	T/B cells	Ad 54kDa E1b$_{384-395}$	**L**RR**G**M**FRPSQ**C**N**	A-gliadin$_{206-217}$	**L**GQ**G**S**FRPSQ**Q**N**	-	[45]
GBS	IV infection / vaccination	B cells	IV HA	–	GM1	–	´–	[108]
Myocarditis	Ad, IV, RSV, CV	T cells	CV	–	MYHC-α$_{334-352}$	DSAFDVLSFTAEEKAGVYK	–	[129]
		B cells	CV	–	Collagen IV, actin fibronectin, others	–	Multiple homologies between CV and Col IV	[130]
Narcolepsy	IV infection / vaccination	B cells	IV A NP$_{111-121}$ [GM3; TRIB2]	**YD**K**EE**IRRI**WR**	HCRTr$_{234-45}$	**YD**D**EE**FL**R**YL**WR**		[111]
Neuro-psychiatric	IV	B cells	IV HA	Various	AGP	Various	Potential cross reactivity, based on sequence alignment	[119]
			IV		NMDA A2			[120]
								[122]
	SARS-CoV, IV	B cells	Various	Various	ACTH	Various		
SS	CV	B cells	CV A21/A13 2B protein	MVTSTI**TEKLLK**N**L**VKI MVTSVL**TEKLLK**N**L**IKI	Ro60 kDa$_{216–232}$	KALSVE**TEKLLK**Y**L**EAV		[134]
T1DM	CV	B cells	IV HA (mAbs)	–	Pancreatic α-cells	–	Tissue staining with mAbs	[140]

ACTH, Adrenocorticotropic hormone; ADEM, Acute disseminated encephalomyelitis; Ad, Adenovirus; AGP, Axon guidance proteins; CD, Celiac disease; Col IV, Collagen IV; CoV, Coronavirus; CV, Coxsackie virus; GBS, Guillain-Barré Syndrome; GM1, Monosialotetrahexosylganglioside; GM3, Monosialodihexosylganglioside; HA, Hemagglutinin; HCRTr2, Hypocretin Receptor 2; IV, Influenza virus; HPIV, Parainfluenza virus; mAbs, monoclonal antibodies; MBP, Myelin Basic Protein; MOG, Myelin Oligodendrocyte Glycoprotein; MYHC-a, cardiac myosin heavy chain-a; NA, Neuraminidase; NMDA, A2 N-methyl-D-aspartate receptor A2 subunit; ORF, Open reading frame; RSV, Respiratory syncytial virus; SS, Sjögren Syndrome; TRIB2, Tribbles homolog 2; T1DM, Type 1 diabetes mellitus

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Narcolepsy

Narcolepsy was associated with the IV A(H1N1) pdm09 vaccine Pandemrix® (GlaxoSmithKline, London, UK) [109] and also with A(H1N1)pdm09 infection [110]. Recently, Ahmed et al. [111], showed that the Pandemrix® vaccine, in some HLA-DQB1*06:02-positive individuals, induced IV A $NP_{111-121}$ antibodies, which were cross-reactive to the hypocretin receptor 2_{34-45} (**Tab. 2**). Although hypocretin receptor 2 autoantibodies were detected in 85 % of patients with Pandemrix®-associated narcolepsy [111], the exact mechanism of the antibody-induced narcolepsy remains to be determined.

Other autoantibodies with a potential link to narcolepsy are anti-monosialodihexosylganglioside (GM3) [112] – and anti-Tribbles homolog 2 (TRIB2) [113] antibodies. Anti-GM3 antibodies were detected more frequently in patients with Pandemrix®-associated narcolepsy than in vaccinated healthy controls [112], whereas no such correlation was evident for anti-TRIB2 antibodies after Pandemrix® vaccination [114]. Nonetheless, anti-TRIB2 antibody titers were found to be increased in narcolepsy patients, compared to controls [113]. Furthermore, transfer of pooled anti-TRIB2 positive IgG samples from the blood of narcolepsy patients into mice resulted in narcolepsy-like symptoms and orexin-neuron loss [115].

Other neurologic/neuropsychiatric disorders

Anti-N-methyl-D-aspartate receptor (NMDAR) antibodies were detected in patients with herpes simplex encephalitis [116], although results are inconsistent [117]. These findings suggest that infections are a possible trigger for psychiatric diseases.

Maternal infection, including influenza, has been suggested to play a role in the development of psychiatric disorders in the child [118]. Lucchese et al. identified influenza epitope mimics in multiple neuronal proteins ([119, 120]; **Tab. 2**). Cross-reactivity might lead to neuropsychiatric disorders, although experimental verification is needed.

Other autoantibodies, which may play a role in neuropsychiatric disorders, such as anorexia nervosa, chronic fatigue syndrome or major depression, are anti-adrenocorticotropin (ACTH) antibodies [121], which may cause ACTH deficiency. Wheatland proposed that SARS-CoV infection can induce pathogen-specific antibodies, which are cross-reactive to ACTH ([122]; **Tab. 2**).

Celiac disease (CD)

Gastrointestinal infections and to a lesser extent also respiratory infections in early life increased risk of developing CD [123]. Ad may contribute to CD development. A sequence mimic of the A-gliadin $protein_{206-217}$ has been identified in the 54 kilodalton (kDa) E1b protein of Ad $12_{384-395}$ [45]. Rat antiserum generated against the $E1b_{384-395}$ epitope cross-reacted with A-gliadin as well as a synthetic $A\text{-}gliadin_{211-217}$ peptide ([45]; Table 2). CD patient serum antibodies were also shown to react to a synthetic A $gliadin_{212-217}$ peptide [124]. Furthermore, T cell cross-reactivity to a synthetic peptide resembling the A-gliadin/E1b sequence have been detected in CD patients [125]. These results were inconsistent in follow-up studies [126].

Myocarditis

Infectious myocarditis is caused by different pathogens, including respiratory viruses such as Ad, IV, RSV and CV [98, 127]. Viral and immune mechanisms contribute to disease onset and persistence in myocarditis [127]. Massilamany et al. [128] showed that immunization of A/J mice with peptide mimics of cardiac myosin heavy chain (MYHC)-$\alpha_{334-352}$ induced cross-reactive T cells and led to the development of myocarditis. Additionally, CV B3 infection led to the generation of such MYHC-$\alpha_{334-352}$-reactive $CD4^+$ T cells and associated myocarditis in A/J mice ([129]; **Tab. 2**). Different antibodies, including those against cardiac myosin and actin, are associated with myocarditis [127]. CV mimics sequences of actin, myosin, collagen and laminin [130]. Moreover, anti-CV antibodies were shown to bind to actin, collagen IV and fibronectin [130].

Sjögren's syndrome (SS)

Viral infections, including CV have been suggested to play a role in the development of SS [131]. In SS, antibodies and/or T cells to different autoantigens, frequently Ro (SSA) and La (SSB) are present [132, 133]. Sequence homologies between the 2B protein of CV A21/A13 and the Ro60 kDa antigen may induce cross-reactive autoantibodies. Stathopoulou et al. [134] showed that serum of SS patients recognized synthetic peptides from the homologous regions of both proteins more frequently than serum of systemic lupus erythematosus (SLE) patients or controls. Cross-reactivity was confirmed in inhibition assays, using both synthetic peptides ([134]; **Tab. 2**). Mimics of Ro60 kDa T cell epitopes have been identified in various bacteria from the human skin, oral cavity, intestine and vaginal flora [135]. Peptide mimics were able to stimulate Ro60 kDa-reactive T cells [135].

Type 1 diabetes mellitus (T1DM)

Development of T1DM has been linked to different viral infections, especially enterovirus infection. Also respiratory viral infections, including IV may be associated to T1DM [136]. One possible mechanism, contributing to autoimmunity in T1DM is molecular mimicry [44, 137]. CMV or rotavirus infection may induce cross-reactive T cells to pancreatic autoantigens [138, 139], whereas for coxsackie virus (CV) such findings are inconsistent [137].

Recently, Qi et al. [140] stained pancreatic tissue with monoclonal antibodies specific for different influenza HA epitopes. Two distinct antibodies were cross-reactive to human pancreatic α-cells, but not β-cells (**Tab. 2**). As shown before in mice, after almost complete diphtheria toxin-induced β-cell loss, pancreatic α-cells are able to differentiate into insulin producing cells [141]. If pancreatic α cells are the progenitors to β-cells, influenza-induced antibodies against α-cell antigens eventually result in the onset of diabetes.

Asthma/allergy

About 300 million people are currently affected by asthma worldwide [142], while the prevalence might rise to 1 billion in 2050 [143]. Characteristics of asthma are chronic airway inflammation, airway hyperreactivity, over production of mucus and remodelling of airways, which becomes relevant particularly in chronic disease.

One major risk factor for the development of asthma are recurrent wheezing episodes early in life, which are caused by viruses in 62–98 % [144, 145] of cases. RSV-or RV-induced wheezing in children < 3 years, with at least one asthmatic parent, was associated with an increased risk for asthma at 6 years of age [146]. Recently, Lukkarinen et al. [145] followed up children with a severe wheezing episode for 7 years. They identified RV-induced wheezing, sensitization and eczema as risk factors for the development of atopic asthma, whereas non-atopic asthma risk factors included first wheezing at < 12 months of age caused by viruses other than RV/RSV and parental smoking. Early onset asthma can resolve spontaneously, but recurrent infections with respiratory viruses over time makes spontaneous resolution less likely [10]. Therefore, viral respiratory tract infections also contribute to the persistence of asthma.

Most asthma exacerbations are also caused by respiratory viral infection, such as RV, RSV, IV, CoV, HMPV, parainfluenza virus and adenovirus [144]. RV is the pathogen detected most frequently in all age groups, whereas RSV affects mostly preschool children and IV is most prevalent in adults [144].

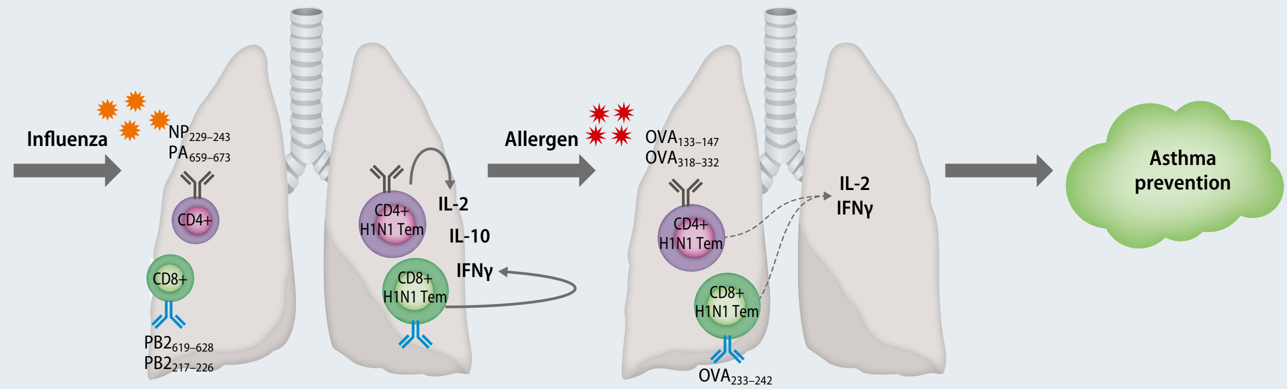
On the other hand, the prevailing concept to explain the rising prevalence of allergic and autoimmune diseases in industrialized countries is the hygiene hypothesis [147]. According to the latter, less frequent exposure to pathogens in early life is associated with the development of allergies [148]. Protective effects of bacteria or bacterial products on asthma development have been well characterized [148], but also viruses [149] as well as respiratory viruses, including IV [150], were shown to protect mice from asthma. Correlates of protection are induction of T1 immune responses, e.g. by stimulation of innate immune receptors, such as Toll-like receptors [148, 151]. Viral infections were shown to protect from asthma by induction of an natural killer T (NKT) cell subset [150] or monocytes with a regulatory phenotype [149].

Our group further examined the role of respiratory viral infection on asthma protection in a murine model. In agreement to earlier reports [150, 152], we found that IV A infection of Balb/c mice confers protection against ovalbumin (OVA)-induced, but also house dust mite (HDM)-induced asthma. Protection was dependent on $CD4^+$ and $CD8^+$ T_{em} cells, which were cross-reactive to IV A- and OVA-derived peptides, as predicted by bioinformatics analysis. Upon *ex vivo* restimulation with the predicted influenza A- or OVA-derived peptides, lung T cells showed increased production of IL-2 and IFNγ. Furthermore, peptide immunization with the predicted virus-derived peptides also provided asthma protection through T_{em} cells. This is possibly due to the production of IFNγ by virus-specific T cells upon allergen challenge, as an augmented IFNγ response can protect from experimental asthma [152]. Thus, we provide evidence for T_{em}-mediated HI between viruses and allergens as a protective mechanism against allergic asthma ([153]; **Fig. 2)**.

Conclusions and Outlook

HI involving respiratory viruses may have various protective, but also detrimental effects on the host. Because of differences in the private TCR repertoire, the clinical outcome of cross-reactivity between the same epitopes may be detrimental in one and beneficial in another person, as seen for example between IV and EBV [48, 85]. IV vaccination has been associated with autoimmune diseases in a few cases [94, 107, 109]. Nevertheless, an association between autoimmune disease and respiratory viral infection has been more extensively discussed. Different approaches for broadly protective vaccines are currently under investigation. Some vaccines were shown to induce lung T_{rm} cells, the role of which in heterologous protection from respiratory tract infections is yet to be determined in humans.

Our group showed that HI between respiratory viruses and allergens protects from experimental asthma [153], thus expanding the hygiene hypothesis. Further studies are needed to determine whether HI is a broadly applicable concept between other respiratory viruses and environmental allergens. Moreover, it will be interesting to see whether any of the currently licenced or future vaccines has the potential to induce heterologous protection



H1N1 Influenza, H1N1 virus strain; IL, Interleukin; IFN, Interferon; NP, Nucleoprotein; OVA, Ovalbumin; PA, Polymerase acidic protein; PB2, Polymerase basic protein 2; T_{em}, T effector memory cells

Fig. 2: Influenza-mediated prevention of allergic airway inflammation was identified in two murine models of OVA- and house dust mite-induced experimental asthma. Transfer experiments revealed that protection was dependent $CD4^+$ and $CD8^+$ T_{em} cells. *Ex vivo* stimulation of lung T_{em} cells from H1N1-infected animals resulted in enhanced IFNγ and IL-10 release. An in silico analysis identified four influenza- and three OVA-derived potentially cross-reactive candidate T-cell epitopes. Immunization with a mixture of these identified influenza peptides conferred asthma protection. These results illustrate heterologous immunity of virus-infected subjects towards allergens, and extend the hygiene hypothesis.

from viral infection as well as asthma. Recently, gammaherpesvirus infection was shown to induce regulatory monocytes, which prevented experimental asthma in mice [149]. Therefore, heterologous innate immune stimulation with tolerogenic or T1 promoting adjuvants [14] might be utilised to induce allergen tolerance (**Fig. 3**).

Appendix

Glossary

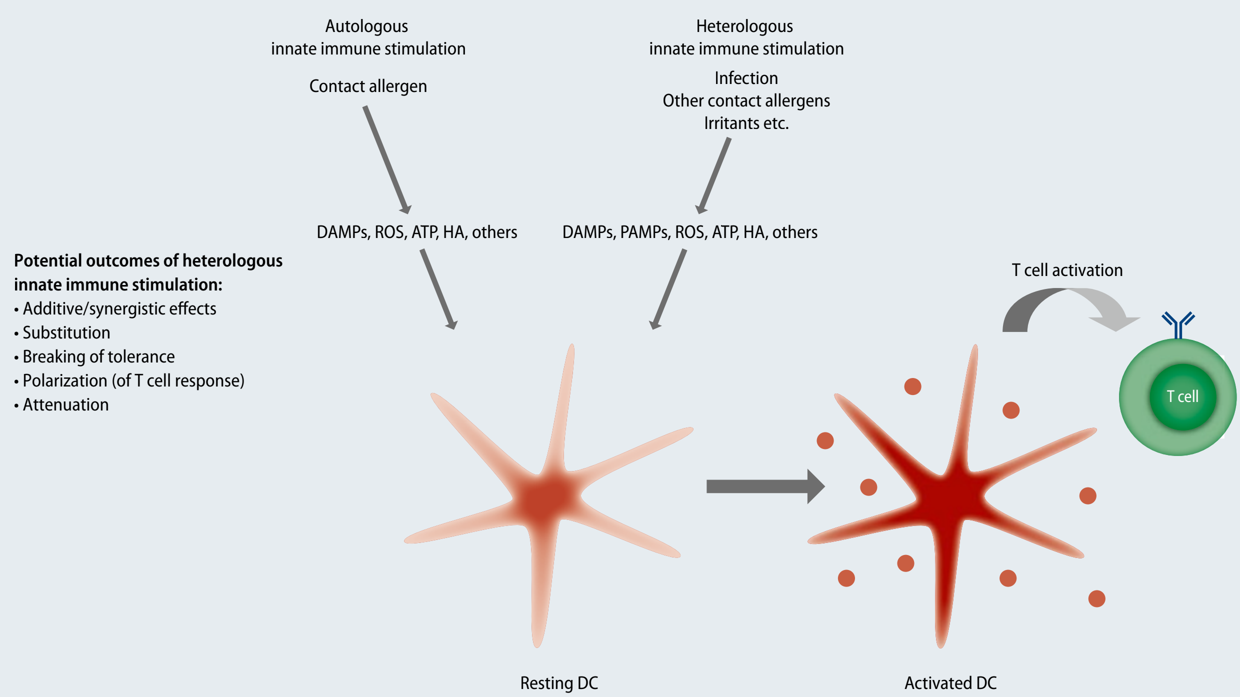
Acute disseminated encephalomyelitis (ADEM): ADEM is a rare autoimmune disease affecting the central nervous system (CNS), with an incidence of 0.6–0.8/100,000 people/year [94]. Especially young children suffer from ADEM, but adults may also be affected. ADEM is an autoimmune mediated, demyelinating disease of the central nervous system (CNS) with a usually monophasic course. Clinically, a vast array of neurological symptoms is possible, from varying focal deficits to encephalopathy (confusion, reduced consciousness, irritability).

Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis: Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis belongs to the heterogeneous group of autoimmune epilepsies, which mainly occur as paraneoplastic syndromes [154]. Antibodies directed against cancer antigens are thought to cross-react with neuronal antigens.

Celiac disease (CD): Prevalence of CD in the European population is approximately 1 % [155]. Genetically susceptible individuals with a genetic background of HLA-DQ2 and/or HLA-DQ8, usually develop symptoms at childhood, although disease onset may occur later in life. Different infections are thought to promote or prevent CD development [156].

Computationally optimized broadly reactive antigen (COBRA) HA: The HA amino acid compositions from many isolated IV A strains is analysed. The aim is to define a consensus sequence for every amino acid in the HA protein.

Guillain-Barré syndrome (GBS): GBS is a rare neurological disease with an incidence of 0.4–4/100,000 people per year [106]. Classical GBS, also called acute inflammatory demyelinating polyneuropathy (AIDP), is caused by an autoimmune demyelination of peripheral nerves, which leads to subacute ascending paralysis with muscle weakness and sensory deficits in the limbs. Severe cases can present with respiratory failure or autonomic instability. Axonal forms of GBS, namely AMAN and AMSAN are associated with anti-GM1 and/or anti GD1a antibodies, while in Miller Fisher syndrome and to a lesser extent also in Bickerstaff brainstem encephalitis, anti-GQ1b antibodies are found. No antibody specific for AIDP has been detected yet.



ACD, Allergic contact dermatitis; ATP, Adenosine triphosphate; DAMP, Damage-associated molecular patterns; DC, Dendritic cell; HA, Hyaluronic acid; PAMP, Pathogen-associated molecular patterns; ROS, Reactive oxygen species; PRR, Pattern recognition receptors

Fig. 3: Example of heterologous innate immune stimulation in ACD. Contact allergens are able to trigger PRRs directly or indirectly by the release of mediators. Heterologous innate immune stimuli, such as infections or irritants can enhance innate immune activation and therefore promote the development of a contact allergen-specific T cell response and ACD. Allergen-specific T cells are usually raised against the autologous innate immune stimulus (contact allergen), while heterologous innate immune stimuli in most cases do not trigger a T cell response. (Adapted from Martin SF [14])

Heterologous innate immune stimulation: The "original" or homologous pathogen/antigen often induces an adaptive immune response. Heterologous pattern recognition receptor (PRR) ligands stem from other sources than the original antigen and mostly do not induce adaptive immune responses. Heterologous PRR stimulation alters the immune response towards the homologous antigen. PRR ligands include various substances, such as vaccine adjuvants, other pathogens or commensal bacteria and endogenous ligands (e.g. hyaluronic acid) [14].

Heterosubtypic immunity: Immunity towards one virus also provides heterologous immunity against a substrain of the first virus. The term heterosubtypic immunity is mostly used when referred to IV A infection.

Heterologous immunity (HI): The immune response towards one antigen alters the immune response towards a subsequent encounter with an unrelated antigen. This involves allo-, auto- or allergen-derived antigens as well as pathogen-derived antigens. Heterologous antigen encounter may have protective or detrimental effects on the host.

Myocarditis: The initial phase of the disease is thought to be mediated by direct myocardial damage through distinct agents (e.g. infection, toxins, drugs), which is followed by an immune mediated phase. Ongoing infection and/or autoimmune disease leads to chronic myocarditis [127]. Myocarditis can result in dilated cardiomyopathy or sudden cardiac death [127].

Narcolepsy: Narcolepsy is characterized by daytime sleepiness, cataplexy and sleep attacks and affects about 30 per 100,000 people [109]. Loss of hypocretin (orexin)-producing neurons in the hypothalamus is characteristic for type 1 narcolepsy, but not for type 2 narcolepsy. Disease onset is typically between 10 and 30 years of age [109]. About 98% of patients with narcolepsy and cataplexy are HLA-DQB1*06:02 positive, which suggests a role for T cells in disease pathogenesis [109].

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Pandemrix®: Pandemrix® is a monovalent A(H1N1) pdm09 vaccine. It was broadly used in Europe during the 2009 swine flu pandemic. Pandemrix contained much higher doses of NP than other A(H1N1)pdm09 vaccines [111].

Paratope: The antigen binding region of an antibody contains multiple paratopes, which recognize their epitope on a given antigen.

Private TCR repertoire: The public TCR repertoire consists of T cell clones, which are identical for all individuals, whereas T cell clones, which are unique for an individual form the private TCR repertoire. The private TCR repertoire leads to variability in immune recognition and cross-reactivity phenomena. For example, the recognition of the same epitopes by different T cells may result in detrimental or beneficial disease outcomes in the respective hosts.

Sjögren's syndrome (SS): SS is characterized by lymphocyte infiltration of salivary glands (SGL). Decreased SGL function causes xerostomia and xerophthalmia.

T cell receptor (TCR) cross-reactivity: The ability of the TCR to recognize more than one antigen is referred to as TCR cross-reactivity.

Type 1 diabetes mellitus (T1DM): T1DM is characterized by autoimmune mediated loss of insulin-producing β cells in the pancreas, while glucagon-producing α cells and somatostatin producing δ cells are spared. Disease is thought to be T cell mediated, which means that autoreactive T cells attack pancreatic β cells.

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Acknowledgments

The work was supported by the German Research Foundation, SFB 1021, Project C04 and the German Center for Lung Research (DZL)

Conflict of interest

C. Skevaki has received grants from the German Research Foundation, the German Center for Lung Research, Hycor and Mead Johnson Nutritional and consultancy fees by Hycor and Bencard. H. Renz has received a grant from the German Research Foundation and the German Center for Lung Research and payment for lectures from Allergopharma, Novartis, Thermo Fisher, Danone, Mead Johnson Nutritional, and Bencard and has received payment for research and development projects from Hycor, Mead Johnson, and Beckman Coulter. E. Pusch declares no relevant conflicts of interest.

Cite this as

Pusch E, Renz H, Skevaki C. Respiratory virus-induced heterologous immunity – Part of the problem or part of the solution? Allergo J Int 2018,27:79–96
https://doi.org/10.1007/s40629-018-0056-0

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