Review

Rotavirus and autoimmunity

J. Gómez-Rial [a,b,*], I. Rivero-Calle [a,d], A. Salas [a,c], F. Martinón-Torres [a,d]

[a] *Grupo de Investigación en Genética, Vacunas, Infecciones y Pediatría (GENVIP), Instituto de Investigación Sanitaria de Santiago (IDIS) and Hospital Clínico Universitario and Universidade de Santiago de Compostela (SERGAS), Travesa da Choupana s/n 15706 Galicia, Spain*
[b] *Laboratorio de Inmunología, Servicio de Análisis Clínicos, Hospital Clínico Universitario Santiago de Compostela (SERGAS), Travesa da Choupana s/n 15706 Galicia, Spain*
[c] *Unidade de Xenética, Instituto de Ciencias Forenses, Facultade de Medicina, Universidade de Santiago de Compostela, and GenPoB Research Group, Instituto de Investigaciones Sanitarias (IDIS), Hospital Clínico Universitario de Santiago (SERGAS), Travesa da Choupana s/n 15706 Galicia, Spain*
[d] *Translational Pediatrics and Infectious Diseases, Department of Pediatrics, Hospital Clínico Universitario de Santiago de Compostela, Travesa da Choupana s/n 15706 Galicia, Spain*

A R T I C L E I N F O

S U M M A R Y

Rotavirus, a major etiological agent of acute diarrhea in children worldwide, has historically been linked to autoimmunity. In the last few years, several physiopathological approaches have been proposed to explain the leading mechanism triggering autoimmunity, from the old concept of molecular mimicry to the emerging theory of bystander activation and break of tolerance. Epidemiological and immunological data indicate a strong link between rotavirus infection and two of the autoimmune pathologies with the highest incidence: celiac disease and diabetes. The role for current oral rotavirus vaccines is now being elucidated, with a so far positive protective association demonstrated.

© 2020 The Author(s). Published by Elsevier Ltd on behalf of The British Infection Association.
This is an open access article under the CC BY-NC-ND license.
(http://creativecommons.org/licenses/by-nc-nd/4.0/)

Introduction

Rotavirus is the leading cause of acute gastroenteritis in infants and young children worldwide.[1] It is a major cause of mortality in low-income countries and a significant cause of morbidity in developed countries.[2] Rotavirus genus is constituted by nine species (from A to I), however only rotavirus A cause more than 90% of rotavirus infections in humans[3]

The rotavirus genome is formed by 11 dsRNA segments that codes for six structural and six nonstructural proteins.[4] Structural proteins form the rotavirus particle and are called based on their molecular weight as VP1, VP2, VP3, VP4, VP6 and VP7. In addition, nonstructural proteins are only produced during cell infection and are called NSP1, NSP2, NSP3, NSP4, NSP5 and NSP6. Rotavirus structure and location and function of viral proteins are summarized in Fig. 1.

Rotavirus infects intestinal cells and cause gastroenteritis; however, infection is not limited to the intestinal mucosa, and systemic viral dissemination has been widely demonstrated.[5–8] Thus, recent studies have described how rotavirus infection can affect a wide spectrum of targets including the nervous system, liver, pancreas, etc.; the term "gastroenteritis by rotavirus" is therefore giving way to a broader concept of "disease by rotavirus".[9]

Traditionally, the main extraintestinal manifestations linked to rotavirus infection have been neurological, namely, the development of convulsions. However, during recent years, rotavirus has also been proposed as a viral trigger for the development of autoimmune diseases, such as celiac disease (CD) and type-1-diabetes (T1D).[9] The concept of a viral trigger for the development of autoimmune diseases is not new, since behind almost all autoimmune processes underlies an infectious pathogen, viral or bacterial. Several mechanistic explanations have been proposed. The present review aims at revisiting all existing theories linking rotavirus infection with autoimmune processes.

In addition, two rotavirus vaccines were licensed in 2006 for the pediatric population worldwide. One monovalent vaccine (Rotarix® manufactured by Glaxosmithkline SL) and one pentavalent vaccine (RotaTeq® manufactured by Merck and Co Inc). Both vaccines have demonstrated a great impact on rotavirus infection burden, showing a marked reduction on diarrhea hospitalization rates after their introduction;[10–13] the impact of these vaccines on the extraintestinal manifestations and the development of autoimmune diseases is the subject of ongoing research[9]

* Corresponding author at: Grupo de Investigación en Genética, Vacunas, Infecciones y Pediatría (GENVIP), Instituto de Investigación Sanitaria de Santiago (IDIS) and Hospital Clínico Universitario and Universidade de Santiago de Compostela (SERGAS), Travesa da Choupana s/n 15706 Galicia, Spain.
E-mail address: jose.gomez.rial@sergas.es (J. Gómez-Rial).
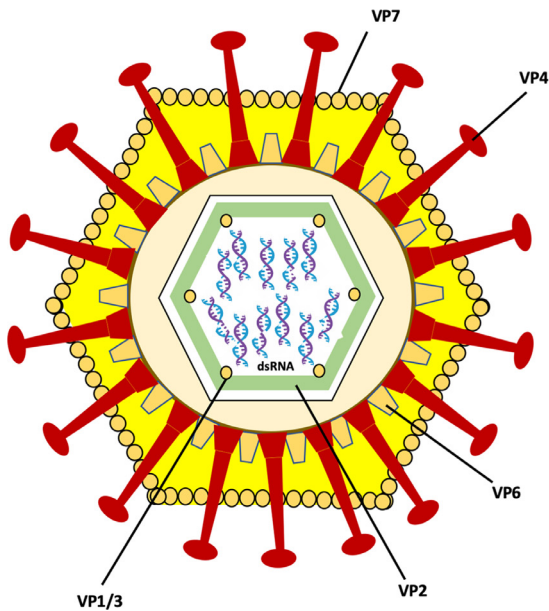
Protein	Molecular weight (Kdal)	Location	Function
VP1	125	Vertices of inner capsid	RNA-dependent RNA polymerase
VP2	102	Inner capsid	RNA binding
VP3	88	Vertices of inner capsid	Viral mRNA capping enzyme
VP4	87	Outer capsid	Spike protein, cell attachment
NSP1	59	Nonstructural	Antagonist of host IFN response
VP6	45	Intermediate capsid	Structural
NSP2	37	Nonstructural	NTPase and RNA-binding; formation of viroplasm
NSP3	35	Nonstructural	Facilitate translation of rotaviral mRNA transcripts and shut-off of cellular protein synthesis
VP7	34	Outer capsid	Structural and neutralizing antigen
NSP4	20	Nonstructural	Intracellular receptor for newly viral particles; Enterotoxin
NSP5	22	Nonstructural	Binding partner of NSP2 in the formation of viroplasms
NPS6	22	Nonstructural	Viral genome replication and packaging

Fig. 1. Diagram showing rotavirus structure, proteins location and functions
Rotavirus particle consist of 11 unique double helix molecules of RNA (dsRNA) surrounded by a non-enveloped three-layered protein capsid (inner, intermediate and outer). Six structural viral proteins (VPs) form the virus particle (VP1–VP7); in addition to this VPs, there are six nonstructural proteins (NSPs) only produced during cell infection (NSP1–NSP6).

Epidemiology of rotavirus gastroenteritis

Rotavirus infects almost every child globally by 3–5 years of age.[14] In 2016, more than 258 million cases of rotavirus infection were reported in children < 5 years globally, with an incidence of 0.42 cases per child-year. It was responsible for an estimated 128,500 deaths throughout the world, the 29.3% representing diarrheal deaths among children younger than 5 years.[15] Rotavirus is highly contagious among children and repeated infections with different viral strain are possible with several episodes of gastroenteritis in the first year of life. The incubation period lasts approximately two days and infection can last for 10 days. Infection may be asymptomatic, may cause self-limited watery diarrhea, or may result in severe dehydrating diarrhea with vomiting, fever and abdominal pain. Rotavirus is transmitted by fecal-oral contact and by contaminated surfaces and hands, and also respiratory spread.[16]

Rotavirus affects populations in all socioeconomic groups and is equally prevalent in industrialized and developing countries; however, due to limited access to health care, lack of hydration therapy and greater prevalence of comorbidities, >90% mortality occurs in low-income countries.[17] Rotavirus infection typically occur during the winter months of the year in temperate regions, while year-round patterns are common in the warmer tropical regions.[18] However, infection can occur anytime of the year.

Viral trigger for autoimmune diseases

Autoimmune processes are produced by alterations in the normal immune homeostasis. Tolerance is a fundamental property of the immune system and involves the self vs. non-self-discrimination and the ability to recognize and respond only to foreign antigens.[19] Autoimmunity is produced when this tolerance to self-antigens is lost: host immune system considers an innocuous self-component as a potential threat and initiates an auto-aggression.

Multiple factors are thought to contribute to the autoimmune response, including genetics, immune regulation, age and environment.[20] Sex is also an influencing factor, supported by the observation of the striking female predominance for most of autoimmune diseases.[21] Sex bias might be originated by differential sex hormones, fetal microchimerism or skewed X chromosome inactivation.[22] Infectious pathogens including viruses and bacteria are considered the main environmental triggers,[23–25] while changes in the intestinal virome precede the development of autoimmunity.[26] Four mechanisms have been proposed to explain how pathogen infection can lead to autoimmunity: molecular mimicry, bystander activation, epitope spreading, and cryptic antigens.

According to the theory of molecular mimicry,[27] some components in the pathogen structure or in the aminoacidic composition may be similar to those of the host. In these cases, immune cells are initially activated in response to the pathogen during infection but later, by a mechanism of cross-reactivity, they recognize the self-components as a potential threat and generate an autoimmune response.

Instead, the bystander activation model[28] propose that the inflammatory environment produced during infection causes a loss of self-tolerance and a non-specific activation of autoimmune cells.

According to the model of epitope spreading,[29] an immune response to a chronic infection can cause damage to self-tissue and release self-antigens to the medium. Phagocytic cells under an inflammatory environment capture these antigens and this can initiate a self-immune response.

Lastly, infection can lead to autoimmunity through the presentation of cryptic antigens.[30] Under normal conditions, these antigens are not exposed to the immune system. However, an inflammatory reaction increases the action of proteases and may lead to a differential processing and presentation of self-antigens that induces an autoimmune response.

Overall, autoimmune diseases are mainly multifactorial processes where genetics, immune regulation and environmental factors such as viral infections are key players. Determine the burden
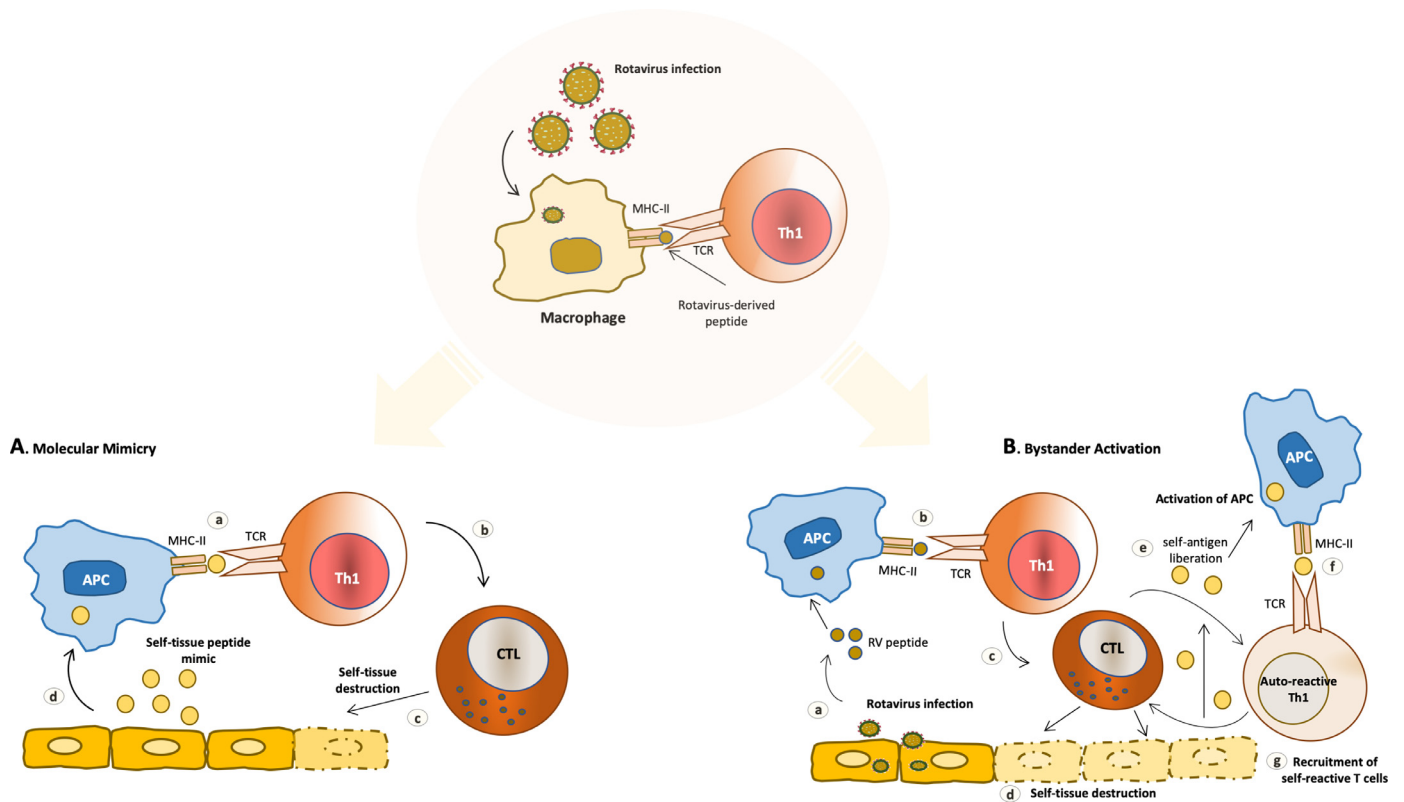
Fig. 2. Mechanisms proposed for rotavirus-triggered autoimmunity

After rotavirus infection, activated immune cells (Th1) migrate to the infected organ and can trigger autoimmunity through these proposed mechanisms:

(A) The **Molecular Mimicry** model describes the activation of cross-reactive Th1 cells that recognize both the rotavirus peptide and the self-peptide: (a) activation of the cross-reactive Th1 cells results in the release of cytokines and chemokines, (b) which recruit and activate cytotoxic T cells (CTL), in turn mediating self-tissue damage; (c) the subsequent release of self-tissue antigens activates APCs and (d) perpetuates the autoimmune process.

(B) The **Bystander Activation** model involves the nonspecific activation of self-reactive Th1 cells. (a) and (b) activation of rotavirus-specific Th1 cells leads to inflammation, and (c) results in the increased infiltration of cytotoxic T cells (CTL), (d) which mediates self-tissue destruction and (e) liberation of self-antigen, and (f) the activation of self-reactive Th1 cells by a TCR-dependent mechanism; (g) self-reactive T cells activated in this manner mediate self-tissue damage and perpetuate the autoimmune response.

of each of these components is complex and varies according to the autoimmune disease.

Rotavirus infection as trigger for autoimmune processes

Two mechanisms have been proposed specifically for rotavirus infection to trigger autoimmunity: molecular mimicry and bystander activation (Fig. 2).

Rotavirus was proposed for the first time 20 years ago as a potential environmental agent in T1D.[31] The mechanism proposed was molecular mimicry of human rotavirus capsid antigen VP7 with the auto-antigen tyrosine phosphatase IA-2 (islet cell antigen 512), i.e. the molecular target of pancreatic islet autoimmunity in T1D. Authors showed that the dominant epitope (805 aminoacids) from the intracytoplasmic domain of IA-2 antigen shared 56% identity with a sequence in rotavirus VP7.[31] In the same study, other viruses could not be discarded as responsible for the autoimmunity response, because the authors also found homology of IA-2 antigen with peptides from herpes, rhino, hanta and flaviviruses. The role for VP7 in the acceleration of diabetes was also demonstrated in non-obese diabetic (NOD) mice infected with Rhesus monkey rotavirus (RVV).[32] Molecular mimicry was also the proposed mechanism to explain the link between rotavirus infection and other autoimmune processes such as celiac disease,[33,34] autoimmune uveitis[35] and murine biliary atresia[36] (Table 1).

Recently, bystander activation and the loss of oral tolerance have been proposed as the mechanisms through which infection by reovirus (the virus family to which rotavirus belongs) triggers

Table 1
Molecular mimicry antigens proposed to induce autoimmunity by rotavirus infection.

Rotavirus protein	Auto-antigen	Pathology	References
VP7	IA-2	T1D	27,31,49
VP7	GAD65	T1D	49
VP7	Transglutaminase	Celiac Disease	33,34
VP4	Retinal S-antigen	Uveitis	35
VP6	Desmoglein-3	Pemphigus vulgaris	74
VP6	Ryanodine receptor	Myasthenia gravis	75
VP4	α-enolase	Biliary atresia	71

the development of celiac disease in genetically predisposed children.[37,38] Intestinal reovirus infection alters the immune response to dietary antigens such as gluten by switching the normal tolerogenic status of intestinal dendritic cells to an inflammatory status that abrogates antigen-specific regulatory T cell responses. Type 1 interferons induced during intestinal reovirus infection were identified as critical nodes in the network of celiac disease susceptibility genes, and the ability to induce high levels of type 1 interferon determines the strains of reovirus associated to the break of tolerance.[38] Previously, this theory of bystander activation mediated by type 1 interferon has been shown to explain the lymphocyte activation observed following rotavirus infection in NOD mice.[39–41] In support to this theory is the coincidence in time of rotavirus infection and the maturation of intestinal immunity in response to solid foods.[37] Early childhood is also the time of life when children are most susceptible to develop celiac disease.

Celiac disease

In 2006, a prospective study carried out in a cohort of USA children genetically susceptible to develop celiac disease, showed that the risk of celiac disease was proportional to the incidence of rotavirus infections.[42] This was the first reported epidemiologic link between rotavirus infection and celiac disease development.

Almost simultaneously, an Italian study in sera from sixty patients suffering active celiac disease showed that a subset of anti-transglutaminase IgA antibodies recognized the rotavirus protein VP7, suggesting a molecular mimicry mechanism to explain the link between rotavirus infection and celiac disease.[33] These auto-antibodies were shown to be functionally active and to have the ability to induce monocyte activation through engagement of toll-like receptor-4 (TLR-4). Moreover, these anti-rotavirus VP7 antibodies were suggested to predict the onset of disease in children previously affected by T1D, preceding the detection of anti-transglutaminase and anti-endomysium antibodies.[34] However, these findings were not corroborated in another study performed in a larger cohort, where it was showed that children with diagnosed celiac disease did not have higher immune reactivity to rotavirus compared to a control group.[43] The molecular mimicry theory to explain the potential trigger effect of rotavirus in celiac disease was questioned, suggesting instead a non-specific response against rotavirus VP7 protein in celiac patients.

Recently, another theory has been proposed, implicating rotavirus as the cause for the oral tolerance breaks in children with celiac disease through a bystander activation effect.[37,38]

The link between rotavirus and celiac disease has recently been extended to the non-celiac gluten sensitivity (NCGS) pathology.[44] This new emerging entity where celiac-specific diagnostic biomarkers are absent, has clinical gastrointestinal and extraintestinal manifestations linked to gluten intake. NCGS is also considered to have an autoimmune origin, and a potential involvement of rotavirus infection in their pathogenesis has also been proposed.

Type 1 diabetes

Rotavirus along with other viruses (e.g. enterovirus) have been historically considered as one of the environmental factors triggering diabetes disease.[31,45–47] Similar to celiac disease, a model of molecular mimicry was initially proposed in the Australian BabyDiab study,[48] where a specific association between rotavirus seroconversion and the increase of T1D associated auto-antibodies (GAD, IA-2 and insulin) was found. Rotavirus infection was then proposed as a trigger for the development of pancreatic islet autoimmunity in genetically susceptible children. A later study reinforced the theory of molecular mimicry between the rotavirus protein VP7 and IA2 and GAD65 peptides, demonstrating how the same epitope sequences in these peptides bind to HLA molecules associated with T1D (HLA-DRB1*04) and have the ability to elicit T cell proliferative responses.[49]

However, a 2-year follow-up of a cohort of children genetically predisposed to diabetes in Finland showed that there was no relationship between rotavirus infection and the development of diabetes-associated auto-antibodies,[50] demonstrating instead the high prevalence of rotavirus antibodies in the population.

Later, in another long follow-up study, enteral infections (including enterovirus, rotavirus and adenovirus) were associated with an enhanced immune response to dietary insulin (e.g. ovine insulin in cow milk).[51] These data suggested a role for enteral infections in the development of beta-cell specific autoimmunity and T1D. These observations were also corroborated in an independent study of a large cohort of 1729 children, the Diabetes Autoimmunity Study in the Young (DAISY), where researchers showed that early childhood enteral infections may increase the risk of islet au-

toimmunity in the presence of existing inflammation induced by diet.[52]

The demonstration that rotavirus infection can exacerbate T1D was proposed in NOD mice with lymphocytic islet infiltration (insulitis).[53] These findings suggested a mechanism of epitope spreading increasing the exposure of beta cells to immune recognition and activation of autoreactive T cells by inflammatory cytokines. Evidence for direct pancreatic rotavirus infection was shown in mice, demonstrating the pathogenic effects of rotavirus on the pancreas *in vivo*, eliciting transient pancreatic involution and hyperglycemia.[54]

Recently, a component of the innate immune response to viral infection, the melanoma differentiation-associated protein 5 (MDA5), was linked specifically to cell death and inflammation in the pancreas of rotavirus-infected mice.[55] Activation of MDA5 limits rotavirus infection through the induction of antiviral interferons and pro-inflammatory cytokines, but it also facilitates the progression to autoimmune destruction of pancreatic beta-cells. Previously, polymorphisms on *IFIH1*, the gene that codes for MDA5, had been found to be associated with the risk of developing T1D.[56–58] Together, these findings support the theory of rotavirus infection as viral trigger for islet autoimmunity, providing data on the mechanism implicated but also indicating a key role for the genetic background of individuals.

Autoimmune uveitis

Autoimmune uveitis (AU) is an inflammatory process of the vascular organ of the eye due to an autoimmune reaction to self-antigens, and it is considered one of the main causes of preventable blindness around the world.[59] Several retinal auto-antigens have been characterized, such as interphotoreceptor retinoid-binding protein (IRBP) and S-antigen (S-Ag).[60] These antigens are under normal condition sequestered in the retinal compartment and are invisible to the immune system. Recently, it was demonstrated that immunity to retinal antigens might occur in the gastrointestinal tract where bacterial antigens activated T-cells, which are cross-reactive with retinal antigens.[61]

Antigenic mimicry of peptide VP4 from rotavirus, alpha-casein from bovine milk and the retinal S-antigen has been described in an experimental autoimmune uveitis rat model.[35,62] According to this theory, rotavirus gastrointestinal infection would induce a breakdown in the oral tolerance to casein from diet and might be able to initiate uveitis in humans. Activated lymphocytes, with the ability to cross the blood-retina barrier, will enter the eye and thus trigger the pathogenic process.

The proposal of milk proteins as key components of the development of autoimmunity is not new.[63–65] Gastrointestinal infection would promote an inflammatory response that could trigger a breakdown of oral tolerance to ingested milk antigens, which mimics with several auto-antigens and develops a cross-reactive pathogenic immune response.

Biliary atresia

Biliary atresia (BA) is a neonatal cholangiopathy of unknown etiology in which one or more bile ducts are blocked.[66] It is a devastating disease that leads to cirrhosis and the need for liver transplantation in the majority of children.[67] One possible etiological theory is the autoimmune origin involving a hepatobiliary viral infection and a subsequently autoimmune-mediated bile duct injury.[68]

A study has proposed rotavirus infection as an initiator in the pathogenesis of experimental BA through the induction of increased nuclear factor-kappa B and abnormal activation of the osteopontin inflammation pathway.[69] Rotavirus nonstructural protein

4 (NSP4) has a pathogenic role as silencing of this gene decreased hepatic injury in animal experiments.[70]

Furthermore, antibodies against α-enolase, a liver enzyme, were found in a mouse model of BA infected with Rhesus rotavirus (RRV) and also in serum samples from patients. Regions of sequence homology between RRV proteins and α-enolase were identified, suggesting that molecular mimicry might activate autoimmunity in BA patients.[71] Adoptive transfer of regulatory T cells (Tregs) in a RRV-infected model of BA was shown to reverse the process and increase survival, suggesting that rotavirus infection might produce dysregulation of Tregs and trigger autoimmunity in murine BA.[72,73]

Other autoimmune diseases

Rotavirus infection has also been linked to other autoimmune diseases through a mechanism of molecular mimicry between rotavirus peptides and auto-antigens. Desmoglein-3 (Dsg3), an auto-antigen described for *pemphigus vulgaris* (a rare chronic blistering skin disease) has been shown to be cross-reactive with rotavirus peptide VP6.[74] Furthermore, a *in silico* study of potential autoimmune threats derived from rotavirus infection using a bioinformatic approach, showed molecular mimicry between rotavirus protein VP6 and the ryanodine receptor, an autoimmune target associated with myasthenia gravis.[75]

Impact of current RV-vaccines on the development of autoimmune diseases

Evidence of the impact of both RV-vaccines on the gastrointestinal disease burden has been reported worldwide since they were licensed.[76,77] Moreover, an impact on childhood seizures was demonstrated by several authors,[9,78–83] showing a vaccine impact beyond the gastro-intestinal disease.

Based on the evidence of the role of rotavirus infection on development of autoimmune diseases, it was hypothesized that vaccination could prevent rotavirus disease and, hence, the development of autoimmunity. However, the potential molecular mimicry effect of rotavirus vaccines similar to those shown in rotavirus infection is yet to be elucidated. Both existing vaccines are live-attenuated; therefore, the same peptides existing in the natural infection are also present in vaccines. Under the hypothesis of molecular mimicry, if rotavirus infection can trigger autoimmune processes, oral vaccination might also cause the same effect. Nevertheless, the absence of an exacerbated intestinal inflammatory component in rotavirus vaccination could avoid the trigger effect elicited by natural infection.

Vaarala et al.[84] carried out a nationwide population-based cohort study after the introduction of systematic rotavirus vaccination in Finland; these authors indicated that rotavirus vaccination was safe in individuals at risk of CD and T1D. They also showed that relative risks for development of T1D and CD were respectively 0.91 and 0.87 when comparing vaccinated to unvaccinated children. These results indicated that oral rotavirus vaccination does not alter the risk of development of autoimmune diseases during 4–6 years of follow-up after vaccination.

At the same time, a 4-year follow-up study also performed in Finland, showed that rotavirus vaccination, together with other factors such as breastfeeding and diet gluten consumption, can modify the risk of celiac disease autoimmunity in children with genetic susceptibility to this autoimmune disorder.[85] Authors showed that risk of CD autoimmunity was reduced in children vaccinated against rotavirus and introduced to gluten before the age of 6 months in a hazard ratio of 0.57. This was the first positive impact finding of rotavirus vaccination on the development of an autoimmune disease.

Very recently, these data were corroborated in an independent study performed also in a Finnish cohort with a period of 11–14 years of follow-up after vaccination.[86] This research showed that the prevalence of CD was higher in non-vaccinated than in vaccinated children (1.11% *vs.* 0.6%, respectively).

A protective association was also reported recently in T1D. An interrupted time-series analysis performed in Australian children comparing 8 years before and after vaccine introduction reported a decrease of T1D cases by 14% in children aged 0–4 years after the introduction of oral RV vaccine, without evidence for change over time in intervention patterns.[87] In the same direction, a recent cohort study developed in USA concluded that rotavirus vaccination was associated to a 33% reduction in the risk of T1D.[88] Furthermore, according these data authors suggested that the pentavalent vaccine was more likely to reduce the risk than the monovalent vaccine.

Further investigations, especially on mechanistic studies, are required in this field but evidence for the potential role of rotavirus vaccination in the prevention of autoimmunity seems to be sufficient to encourage the recommendation of rotavirus vaccine to children genetically predisposed to CD and T1D.

Future perspectives

Our understanding of rotavirus infection has substantially changed in recent years. Beyond the traditional assumption of rotavirus as diarrhea only, rotavirus infection is nowadays considered from a systemic perspective. The traditional epidemiological concept of rotavirus as an environmental trigger for autoimmunity is being re-examined, and several mechanistic approaches are now being proposed. In addition, signaling pathways activated during rotavirus infection and their implications in the autoimmune processes are being elucidated, while it is expected that a better understanding of mechanisms involved in autoimmunity triggering will be helpful to design new therapeutic approaches and public health programs.

The role of current rotavirus vaccines on these important clinical spectra is an active research area. The possibility of preventing celiac and diabetes autoimmunity through oral rotavirus vaccination is exciting. While we await further confirmation, the weight of current evidence is enough to recommend rotavirus vaccination to all children, especially those with family history of autoimmune disease and specially those genetically predisposed. New emerging vaccines, currently in development, will need to be tested on this unforeseen effect.

Declaration of Competing Interest

J. Gómez-Rial, I. Rivero-Calle and A. Salas et al. / Journal of Infection 81 (2020) 183–189

Financial disclosure

References

1. Parashar UD, Gibson CJ, Bresee JS, Glass RI. Rotavirus and severe childhood diarrhea. *Emerg Infect Dis* 2006;**12**(2):304–6.
2. Parashar UD, Hummelman EG, Bresee JS, Miller MA, Glass RI. Global illness and deaths caused by rotavirus disease in children. *Emerg Infect Dis* 2003;**9**(5):565–72.
3. Kirkwood CD. Genetic and antigenic diversity of human rotaviruses: potential impact on vaccination programs. *J Infect Dis* 2010;**202**(Suppl):S43–8.
4. Pesavento JB, Crawford SE, Estes MK, Prasad BV. Rotavirus proteins: structure and assembly. *Curr Top Microbiol Immunol.* 2006;**309**:189–219.
5. Blutt SE, Conner ME. Rotavirus: to the gut and beyond!. *Curr Opin Gastroenterol* 2007;**23**(1):39–43.
6. Blutt SE, Matson DO, Crawford SE, Staat MA, Azimi P, Bennett BL, et al. Rotavirus antigenemia in children is associated with viremia. *PLoS Med* 2007;**4**(4):e121.
7. Ramig RF. Systemic rotavirus infection. *Expert Rev Anti Infect Ther* 2007;**5**(4):591–612.
8. Rivero-Calle I, Gomez-Rial J, Martinon-Torres F. Systemic features of rotavirus infection. *J Infect* 2016;**72**(Suppl):S98–S105.
9. Gomez-Rial J, Sanchez-Batan S, Rivero-Calle I, Pardo-Seco J, Martinon–Martinez JM, Salas A, et al. Rotavirus infection beyond the gut. *Infect Drug Resist* 2019;**12**:55–64.
10. Martinon-Torres F, Bouzon Alejandro M, Redondo Collazo L, Sanchez Lastres JM, Pertega Diaz S, Seoane Pillado MT, et al. Effectiveness of rotavirus vaccination in Spain. *Hum Vaccin* 2011;**7**(7):757–61.
11. Zlamy M, Kofler S, Orth D, Wurzner R, Heinz-Erian P, Streng A, et al. The impact of Rotavirus mass vaccination on hospitalization rates, nosocomial Rotavirus gastroenteritis and secondary blood stream infections. *BMC Infect Dis* 2013;**13**:112.
12. Standaert B, Gomez JA, Raes M, Debrus S, Velazquez FR, Postma MJ. Impact of rotavirus vaccination on hospitalisations in Belgium: comparing model predictions with observed data. *PLoS ONE* 2013;**8**(1):e53864.
13. Hemming-Harlo M, Vesikari T, Uhari M, Renko M, Salminen M, Torcel-Pagnon L, et al. Sustained high effectiveness of RotaTeq on hospitalizations attributable to rotavirus-associated gastroenteritis during 4 years in Finland. *J Pediatric Infect Dis Soc* 2017;**6**(4):317–23.
14. Gurwith M, Wenman W, Hinde D, Feltham S, Greenberg H. A prospective study of rotavirus infection in infants and young children. *J Infect Dis* 1981;**144**(3):218–24.
15. Troeger C, Khalil IA, Rao PC, Cao S, Blacker BF, Ahmed T, et al. Rotavirus vaccination and the global burden of rotavirus diarrhea among children younger than 5 years. *JAMA Pediatr* 2018;**172**(10):958–65.
16. Dennehy PH. Transmission of rotavirus and other enteric pathogens in the home. *Pediatr Infect Dis J* 2000;**19**(10 Suppl):S103–5.
17. Tate JE, Burton AH, Boschi-Pinto C, Parashar UD World Health Organization-Coordinated Global Rotavirus Surveillance N. Global, regional, and national estimates of rotavirus mortality in children <5 years of age, 2000–2013. *Clin Infect Dis: Off Publ Infect Dis Soc Am* 2016;**62**(Suppl 2):S96–S105.
18. Cook SM, Glass RI, LeBaron CW, Ho MS. Global seasonality of rotavirus infections. *Bull World Health Organ* 1990;**68**(2):171–7.
19. Kamradt T, Mitchison NA. Tolerance and autoimmunity. *N Engl J Med* 2001;**344**(9):655–64.
20. Ercolini AM, Miller SD. The role of infections in autoimmune disease. *Clin Exp Immunol* 2009;**155**(1):1–15.
21. Lleo A, Battezzati PM, Selmi C, Gershwin ME, Podda M. Is autoimmunity a matter of sex? *Autoimmun Rev* 2008;**7**(8):626–30.
22. Rubtsova K, Marrack P, Rubtsov AV. Sexual dimorphism in autoimmunity. *J Clin Investig* 2015;**125**(6):2187–93.
23. Getts DR, Chastain EM, Terry RL, Miller SD. Virus infection, antiviral immunity, and autoimmunity. *Immunol Rev* 2013;**255**(1):197–209.
24. Fujinami RS. Can virus infections trigger autoimmune disease? *J Autoimmun* 2001;**16**(3):229–34.
25. Bach JF. Infections and autoimmune diseases. *J Autoimmun* 2005;**25**(Suppl):74–80.
26. Zhao G, Vatanen T, Droit L, Park A, Kostic AD, Poon TW, et al. Intestinal virome changes precede autoimmunity in type I diabetes-susceptible children. *Proc Natl Acad Sci USA* 2017;**114**(30):E6166–E6E75.
27. Kohm AP, Fuller KG, Miller SD. Mimicking the way to autoimmunity: an evolving theory of sequence and structural homology. *Trends Microbiol* 2003;**11**(3):101–5.
28. Fujinami RS, von Herrath MG, Christen U, Whitton JL. Molecular mimicry, bystander activation, or viral persistence: infections and autoimmune disease. *Clin Microbiol Rev* 2006;**19**(1):80–94.
29. Lehmann PV, Forsthuber T, Miller A, Sercarz EE. Spreading of T-cell autoimmunity to cryptic determinants of an autoantigen. *Nature* 1992;**358**(6382):155–7.
30. Lanzavecchia A. How can cryptic epitopes trigger autoimmunity? *J Exp Med* 1995;**181**(6):1945–8.
31. Honeyman MC, Stone NL, Harrison LC. T-cell epitopes in type 1 diabetes autoantigen tyrosine phosphatase IA-2: potential for mimicry with rotavirus and other environmental agents. *Mol Med* 1998;**4**(4):231–9.
32. Pane JA, Dang VT, Holloway G, Webster NL, Coulson BS. VP7 of Rhesus monkey rotavirus RRV contributes to diabetes acceleration in association with an elevated anti-rotavirus antibody response. *Virology* 2014;**468–470**:504–9.
33. Zanoni G, Navone R, Lunardi C, Tridente G, Bason C, Sivori S, et al. In celiac disease, a subset of autoantibodies against transglutaminase binds toll-like receptor 4 and induces activation of monocytes. *PLoS Med* 2006;**3**(9):e358.
34. Dolcino M, Zanoni G, Bason C, Tinazzi E, Boccola E, Valletta E, et al. A subset of anti-rotavirus antibodies directed against the viral protein VP7 predicts the onset of celiac disease and induces typical features of the disease in the intestinal epithelial cell line T84. *Immunol Res* 2013;**56**(2–3):465–76.
35. Wildner G, Diedrichs-Mohring M. Autoimmune uveitis induced by molecular mimicry of peptides from rotavirus, bovine casein and retinal S-antigen. *Eur J Immunol* 2003;**33**(9):2577–87.
36. Mack CL, Tucker RM, Lu BR, Sokol RJ, Fontenot AP, Ueno Y, et al. Cellular and humoral autoimmunity directed at bile duct epithelia in murine biliary atresia. *Hepatology* 2006;**44**(5):1231–9.
37. Brown JJ, Jabri B, Dermody TS. A viral trigger for celiac disease. *PLoS Pathog* 2018;**14**(9):e1007181.
38. Bouziat R, Hinterleitner R, Brown JJ, Stencel-Baerenwald JE, Ikizler M, Mayassi T, et al. Reovirus infection triggers inflammatory responses to dietary antigens and development of celiac disease. *Science* 2017;**356**(6333):44–50.
39. Pane JA, Webster NL, Coulson BS. Rotavirus activates lymphocytes from non-obese diabetic mice by triggering toll-like receptor 7 signaling and interferon production in plasmacytoid dendritic cells. *PLoS Pathog* 2014;**10**(3):e1003998.
40. Pane JA, Fleming FE, Graham KL, Thomas HE, Kay TW, Coulson BS. Rotavirus acceleration of type 1 diabetes in non-obese diabetic mice depends on type I interferon signalling. *Sci Rep* 2016;**6**:29697.
41. Pane JA, Coulson BS. Lessons from the mouse: potential contribution of bystander lymphocyte activation by viruses to human type 1 diabetes. *Diabetologia* 2015;**58**(6):1149–59.
42. Stene LC, Honeyman MC, Hoffenberg EJ, Haas JE, Sokol RJ, Emery L, et al. Rotavirus infection frequency and risk of celiac disease autoimmunity in early childhood: a longitudinal study. *Am J Gastroenterol* 2006;**101**(10):2333–40.
43. Ziberna F, De Lorenzo G, Schiavon V, Arnoldi F, Quaglia S, De Leo L, et al. Lack of evidence of rotavirus-dependent molecular mimicry as a trigger of coeliac disease. *Clin Exp Immunol* 2016;**186**(3):356–63.
44. Puccetti A, Saverino D, Opri R, Gabrielli O, Zanoni G, Pelosi A, et al. Immune response to rotavirus and gluten sensitivity. *J Immunol Res* 2018;**2018**:9419204.
45. Knip M, Akerblom HK. Environmental factors in the pathogenesis of type 1 diabetes mellitus. *Exp Clin Endocrinol Diab: Off J German Soc Endocrinol German Diab Assoc* 1999;**107**(Suppl 3):S93–100.
46. Couper JJ. Environmental triggers of type 1 diabetes. *J Paediatr Child Health* 2001;**37**(3):218–20.
47. Tang JW, Holmes CW. Acute and chronic disease caused by enteroviruses. *Virulence* 2017;**8**(7):1062–5.
48. Honeyman MC, Coulson BS, Stone NL, Gellert SA, Goldwater PN, Steele CE, et al. Association between rotavirus infection and pancreatic islet autoimmunity in children at risk of developing type 1 diabetes. *Diabetes* 2000;**49**(8):1319–24.
49. Honeyman MC, Stone NL, Falk BA, Nepom G, Harrison LC. Evidence for molecular mimicry between human T cell epitopes in rotavirus and pancreatic islet autoantigens. *J Immunol* 2010;**184**(4):2204–10.
50. Blomqvist M, Juhela S, Erkkila S, Korhonen S, Simell T, Kupila A, et al. Rotavirus infections and development of diabetes-associated autoantibodies during the first 2 years of life. *Clin Exp Immunol* 2002;**128**(3):511–15.
51. Makela M, Oling V, Marttila J, Waris M, Knip M, Simell O, et al. Rotavirus-specific T cell responses and cytokine mRNA expression in children with diabetes-associated autoantibodies and type 1 diabetes. *Clin Exp Immunol* 2006;**145**(2):261–70.
52. Snell-Bergeon JK, Smith J, Dong F, Baron AE, Barriga K, Norris JM, et al. Early childhood infections and the risk of islet autoimmunity: the Diabetes Autoimmunity Study in the Young (DAISY). *Diabetes Care* 2012;**35**(12):2553–8.
53. Graham KL, Sanders N, Tan Y, Allison J, Kay TW, Coulson BS. Rotavirus infection accelerates type 1 diabetes in mice with established insulitis. *J Virol* 2008;**82**(13):6139–49.
54. Honeyman MC, Laine D, Zhan Y, Londrigan S, Kirkwood C, Harrison LC. Rotavirus infection induces transient pancreatic involution and hyperglycemia in weanling mice. *PLoS ONE* 2014;**9**(9):e106560.
55. Dou Y, Yim HC, Kirkwood CD, Williams BR, Sadler AJ. The innate immune receptor MDA5 limits rotavirus infection but promotes cell death and pancreatic inflammation. *EMBO J* 2017;**36**(18):2742–57.
56. Looney BM, Xia CQ, Concannon P, Ostrov DA, Clare-Salzler MJ. Effects of type 1 diabetes-associated IFIH1 polymorphisms on MDA5 function and expression. *Curr Diab Rep* 2015;**15**(11):96.

57. Winkler C, Lauber C, Adler K, Grallert H, Illig T, Ziegler AG, et al. An interferon-induced helicase (IFIH1) gene polymorphism associates with different rates of progression from autoimmunity to type 1 diabetes. *Diabetes* 2011;**60**(2):685–90.

58. Liu S, Wang H, Jin Y, Podolsky R, Reddy MV, Pedersen J, et al. IFIH1 polymorphisms are significantly associated with type 1 diabetes and IFIH1 gene expression in peripheral blood mononuclear cells. *Hum Mol Genet* 2009;**18**(2):358–65.

59. Suttorp-Schulten MS, Rothova A. The possible impact of uveitis in blindness: a literature survey. *Br J Ophthalmol* 1996;**80**(9):844–8.

60. de Smet MD, Yamamoto JH, Mochizuki M, Gery I, Singh VK, Shinohara T, et al. Cellular immune responses of patients with uveitis to retinal antigens and their fragments. *Am J Ophthalmol* 1990;**110**(2):135–42.

61. Horai R, Zarate-Blades CR, Dillenburg-Pilla P, Chen J, Kielczewski JL, Silver PB, et al. Microbiota-dependent activation of an autoreactive T cell receptor provokes autoimmunity in an immunologically privileged site. *Immunity* 2015;**43**(2):343–53.

62. Wildner G, Diedrichs-Mohring M. Autoimmune uveitis and antigenic mimicry of environmental antigens. *Autoimmun Rev* 2004;**3**(5):383–7.

63. Stefferl A, Schubart A, Storch M, Amini A, Mather I, Lassmann H, et al. Butyrophilin, a milk protein, modulates the encephalitogenic T cell response to myelin oligodendrocyte glycoprotein in experimental autoimmune encephalomyelitis. *J Immunol* 2000;**165**(5):2859–65.

64. Akerblom HK, Vaarala O, Hyoty H, Ilonen J, Knip M. Environmental factors in the etiology of type 1 diabetes. *Am J Med Genet* 2002;**115**(1):18–29.

65. Vojdani A, Campbell AW, Anyanwu E, Kashanian A, Bock K, Vojdani E. Antibodies to neuron-specific antigens in children with autism: possible cross-reaction with encephalitogenic proteins from milk, Chlamydia pneumoniae and Streptococcus group A. *J Neuroimmunol* 2002;**129**(1–2):168–77.

66. Hartley JL, Davenport M, Kelly DA. Biliary atresia. *Lancet* 2009;**374**(9702):1704–13.

67. Mack CL. The pathogenesis of biliary atresia: evidence for a virus-induced autoimmune disease. *Semin Liver Dis* 2007;**27**(3):233–42.

68. Feldman AG, Tucker RM, Fenner EK, Pelanda R, Mack CL. B cell deficient mice are protected from biliary obstruction in the rotavirus-induced mouse model of biliary atresia. *PLoS ONE* 2013;**8**(8):e73644.

69. Feng J, Li M, Cai T, Tang H, Gu W. Rotavirus-induced murine biliary atresia is mediated by nuclear factor-kappaB. *J Pediatr Surg* 2005;**40**(4):630–6.

70. Feng J, Yang J, Zheng S, Qiu Y, Chai C. Silencing of the rotavirus NSP4 protein decreases the incidence of biliary atresia in murine model. *PLoS ONE* 2011;**6**(8):e23655.

71. Lu BR, Brindley SM, Tucker RM, Lambert CL, Mack CL. alpha-enolase autoantibodies cross-reactive to viral proteins in a mouse model of biliary atresia. *Gastroenterology* 2010;**139**(5):1753–61.

72. Tucker RM, Feldman AG, Fenner EK, Mack CL. Regulatory T cells inhibit Th1 cell-mediated bile duct injury in murine biliary atresia. *J Hepatol* 2013;**59**(4):790–6.

73. Hertel PM, Estes MK. Rotavirus and biliary atresia: can causation be proven? *Curr Opin Gastroenterol* 2012;**28**(1):10–17.

74. Cho MJ, Ellebrecht CT, Hammers CM, Mukherjee EM, Sapparapu G, Boudreaux CE, et al. Determinants of VH1-46 cross-reactivity to pemphigus vulgaris autoantigen desmoglein 3 and rotavirus antigen VP6. *J Immunol* 2016;**197**(4):1065–73.

75. Sarkar T, Das S, Nandy P, Bhowmick R, Nandy A. In silico study of potential autoimmune threats from rotavirus infection. *Comput Biol Chem* 2014;**51**:51–6.

76. Patel MM, Steele D, Gentsch JR, Wecker J, Glass RI, Parashar UD. Real-world impact of rotavirus vaccination. *Pediatr Infect Dis J* 2011;**30**(1 Suppl):S1–5.

77. Aliabadi N, Antoni S, Mwenda JM, Weldegebriel G, Biey JNM, Cheikh D, et al. Global impact of rotavirus vaccine introduction on rotavirus hospitalisations among children under 5 years of age, 2008–16: findings from the global rotavirus surveillance network. *Lancet Glob Health* 2019;**7**(7):e893–903.

78. Payne DC, Baggs J, Zerr DM, Klein NP, Yih K, Glanz J, et al. Protective association between rotavirus vaccination and childhood seizures in the year following vaccination in US children. *Clin Infect Dis: Off Publ Infect Dis Soc Am* 2014;**58**(2):173–7.

79. Pardo-Seco J, Cebey-Lopez M, Martinon-Torres N, Salas A, Gomez-Rial J, Rodriguez-Tenreiro C, et al. Impact of rotavirus vaccination on childhood hospitalization for seizures. *Pediatr Infect Dis J* 2015;**34**(7):769–73.

80. Burke RM, Tate JE, Dahl RM, Aliabadi N, Parashar UD. Rotavirus vaccination is associated with reduced seizure hospitalization risk among commercially insured US children. *Clin Infect Dis: Off Publ Infect Dis Soc Am* 2018;**67**(10):1614–16.

81. Yeom JS, Kim YS, Kim RB, Park JS, Seo JH, Park E, et al. Impact of rotavirus vaccine introduction on rotavirus-associated seizures and a related possible mechanism. *J. Child Neurol* 2015;**30**(6):729–34.

82. Hungerford DJ, French N, Iturriza-Gomara M, Read JM, Cunliffe NA, Vivancos R. Reduction in hospitalisations for acute gastroenteritis-associated childhood seizures since introduction of rotavirus vaccination: a time-series and change-point analysis of hospital admissions in England. *J Epidemiol Community Health* 2019;**73**(11):1020–5.

83. Gomez-Rial J, Sanchez-Batan S, Rivero-Calle I, Pardo-Seco J, Martinon–Martinez JM, Salas A, et al. Further considerations on rotavirus vaccination and seizure-related hospitalization rates. *Infect Drug Resist* 2019;**12**:989–91.

84. Vaarala O, Jokinen J, Lahdenkari M, Leino T. Rotavirus vaccination and the risk of celiac disease or Type 1 diabetes in finnish children at early life. *Pediatr Infect Dis J* 2017;**36**(7):674–5.

85. Kemppainen KM, Lynch KF, Liu E, Lonnrot M, Simell V, Briese T, et al. Factors that increase risk of celiac disease autoimmunity after a gastrointestinal infection in early life. *Clin Gastroenterol Hepato: Off Clin Pract J Am Gastroenterol Assoc* 2017;**15**(5) 694–702 e5.

86. Hemming-Harlo M, Lahdeaho ML, Maki M, Vesikari T. Rotavirus vaccination does not increase type 1 diabetes and may decrease celiac disease in children and adolescents. *Pediatr Infect Dis J* 2019;**38**(5):539–41.

87. Perrett KP, Jachno K, Nolan TM, Harrison LC. Association of rotavirus vaccination with the incidence of type 1 diabetes in children. *JAMA Pediatr* 2019.

88. Rogers MAM, Basu T, Kim C. Lower incidence rate of type 1 diabetes after receipt of the rotavirus vaccine in the United States, 2001–2017. *Sci Rep* 2019;**9**(1):7727.